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TREATMENT SEEKING, TREATMENT ADEQUACY AND OUTCOME OF DEPRESSIVE AND ANXIETY DISORDERS AMONG YOUNG ADULTS IN FINLAND

FINDINGS FROM A POPULATION-BASED SAMPLE

Teija Kasteenpohja

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Auditorium XV, University main building, on 14th December 2018, at 12 noon

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“Nobody cares if you can’t dance well. Just get up and dance. Great dancers are not great because of their technique, they are great because of their passion.”

-Martha Graham

To my family

ABSTRACT

According to previous epidemiological studies, depressive and anxiety disorders are common and tend to be chronic or recurrent. However, they are often under-recognized and undertreated. The incidence of these disorders peaks in late adolescence and early adulthood. Untreated depressive and anxiety disorders may be particularly harmful at this age, since they often limit social, occupational and academic functioning. Therefore, recognition and adequate treatment of depressive and anxiety disorders in adolescence and young adulthood are especially important.

The aims of this study were to describe adequate treatment and outcome of depressive and anxiety disorders in a Finnish general population sample of young adults. Data were derived from the Mental Health in Early Adulthood in Finland (MEAF) study which is a follow-up study of Health 2000 young adult sample, a nationally representative two-stage cluster sample of 1894 Finns aged 18 to 29 years. The follow-up of the MEAF study was carried out as a part of the Health 2011 study. The baseline assessment was conducted in 2003–2005, and the follow-up in 2011.

Criteria for minimally adequate treatment were determined according to evidence-based guidelines and previous studies. Minimally adequate treatment of depressive disorders required antidepressant pharmacotherapy for at least two months with at least four visits with any type of physician a year, or at least eight sessions of psychotherapy/psychosocial support a year or four days of hospitalization. For anxiety disorders, criteria were otherwise the same, but buspirone was also regarded as adequate pharmacotherapy.

This study showed that 76% of young adults with lifetime depressive disorders had had contact with the healthcare system, and 41% of them had received minimally adequate treatment. Women, and those with a substance use disorder, had visited a physician at least once more often than others, while having major depressive disorder was related to visits with a physician at least 4 times a year. Women had also had psychotherapy more often than men. Those with a history of suicidality and lower education dropped out from treatment more often than the rest of the sample. None of the factors were associated with receiving minimally adequate treatment.

Treatment was adequate for 42% of those with a lifetime history of anxiety disorder (excluding those with only a specific phobia), and 71% of them had sought treatment. Comorbid personality disorder was related to benzodiazepine use and misuse, and comorbid substance use with antidepressant or buspirone medication lasting for at least two months. Those who were currently married or cohabiting were less likely than others to have visited a physician at least four times a year. None of the factors were related to minimally adequate treatment or dropping out from treatment.

In the follow-up study, 23% of those with a lifetime depressive and/or anxiety disorder at baseline had these disorders in 2011, whereas the corresponding figure was 10% for those with no DSM-IV diagnosis at baseline. Those with a history of depressive and/or anxiety disorder had poorer self-estimated quality of life and lower level of education compared to the control group in the follow-up.

Sociodemographic factors and treatment were not related to persistence/recurrence of depressive and anxiety disorders, but hypomanic features measured by the Mood Disorder Questionnaire (MDQ) at baseline were associated with worse self-estimated quality of life in the follow-up. Cognitive factors did not either predict the persistence nor recurrence of these disorders. However, those with better neuropsychological test performance at baseline had higher level of education in the follow-up.

This study showed that young adults seek treatment more often than previously, but the lack of adequate treatment is an ongoing problem. Regardless of a tendency for recurrence, the prognosis of depressive and anxiety disorders is relatively favourable, since three-quarters of young adults with a lifetime history of these disorders recovered after six to eight years of follow-up. However, these disorders had an impact on the level of education of affected people in the long term. In the future, barriers to adequate treatment in the healthcare system should be investigated and interventions to remove them should be launched. It is also important that educational policy supports the continuity of education for young people with mental disorders during, and also after, acute episodes.

TIIVISTELMÄ

Epidemiologisten tutkimusten mukaan masennus- ja ahdistuneisuushäiriöt ovat yleisiä, ja usein niillä on taipumus pitkittyä tai uusiutua. Ne ovat kuitenkin alidiagnosoituja ja -hoidettuja. Masennus- ja ahdistuneisuushäiriöiden ilmaantuvuus on korkeimmillaan myöhäisnuoruudessa ja varhaisaikuisuudessa. Hoitamattomat mielenterveyshäiriöt voivat juuri tässä ikävaiheessa rajoittaa yksilön psykososiaalista, akateemista ja ammatillista kehitystä merkittävästi ja olla siten erityisen haitallisia. Siksi niiden tunnistaminen ja asianmukainen hoito tässä ikäryhmässä olisi erityisen tärkeää.

Tässä tutkimuksessa selvitettiin nuorten aikuisten masennus- ja ahdistuneisuushäiriöiden hoidon asianmukaisuutta ja ennustetta Suomessa. Tutkimuksen aineistona käytettiin Nuorten aikuisten terveys ja psyykkinen hyvinvointi (NAPS) -tutkimusta, joka on Terveys 2000 -väestötutkimuksen 1894 tutkittavaa käsittävän 18–29-vuotiaiden nuorten aikuisten aineiston syventävä seurantatutkimus. Pitkäaikaisseurannassa käytettiin Terveys 2011 -tutkimuksessa kerättyjä tietoja. Perustutkimus toteutettiin vuosina 2003–2005 ja seuranta vuonna 2011.

Hoidon asianmukaisuuden kriteerit määriteltiin näyttöön perustuvien hoitosuositusten ja aiempien tutkimusten mukaan. Masennushäiriöiden osalta asianmukainen hoito edellytti vähintään kaksi kuukautta kestävää masennuslääkehoitoa ja neljää lääkärin kannanottoa hoitoon vuoden aikana tai vähintään kahdeksaa psykoterapian tai psykososiaalisen tuen käyntiä vuodessa tai vähintään neljä vuorokautta kestävää sairaalahoitoa masennuksen oireiden vuoksi. Ahdistuneisuushäiriöiden osalta kriteerit olivat muutoin samat, mutta asianmukaiseksi lääkitykseksi hyväksyttiin myös buspironi.

Tutkimus osoitti, että elämänaikaisen masennushäiriö-diagnoosin saaneista nuorista aikuisista 76 %:lla oli ollut hoitokontakti terveydenhuoltojärjestelmään ja 41 % oli saanut asianmukaista hoitoa viimeisimmän masennusjaksonsa aikana. Naisilla ja samanaikaisesta päihdehäiriöstä kärsivillä oli muita useammin vähintään yksi lääkärikäynti ja vakavaa masennustilaa sairastavilla muita useammin vähintään neljä lääkärikäyntiä 12 kuukauden aikana. Naisilla hoitoon oli kuulunut myös tukea antavia keskustelukäyntejä useammin kuin miehillä. Itsemurhaa yrittäneet ja vähemmän koulutetut keskeyttivät hoitonsa muita useammin.

Ahdistuneisuushäiriöitä sairastaneista (poissuljettuina ne, joilla määräkohteinen pelko oli ainoana ahdistuneisuushäiriödiagnoosina) nuorista aikuisista 71 %:lla oli ollut jonkinlainen kontakti terveydenhoitojärjestelmään ja 42 % oli saanut asianmukaista hoitoa viimeisimmän hoitojaksonsa aikana. Samanaikaisella persoonallisuushäiriöllä oli yhteys bentsodiatsepiinien käyttöön ja

väärinkäyttöön, kun taas päihdehäiriö oli yhteydessä yli kaksi kuukautta kestävään masennuslääkkeen tai buspironin käyttöön. Parisuhteessa olevilla oli muita harvemmin vähintään neljä lääkärikäyntiä vuoden aikana.

Pitkäaikaisseurannassa elämänaikaisen masennus- ja/tai ahdistuneisuushäiriö-diagnoosin perustutkimuksen aikana saaneista 23 %:lla oli näitä häiriöitä myös vuonna 2011, kun vastaava luku oli 10 % niillä, jotka eivät perustutkimuksen aikana saaneet mitään DSM-IV-diagnoosia. Häiriöistä kärsineillä oli matalampi koulutustaso ja heikompi itsearvioitu elämänlaatu kuin vertailuryhmässä.

Sosiodemografiset tekijät tai saatu hoito eivät ennustaneet masennus- tai ahdistuneisuushäiriön pysyvyyttä / uusiutumista tai sairastuneiden elämänlaatua pitkäaikaisseurannassa, mutta perustutkimuksen aikana esiintyneillä maanistyyppisillä oireilla, joita arvioitiin Mood Disorder Questionnaire -kyselyllä, oli yhteys heikompaan elämänlaatuun. Myöskään kognitiivisilla muuttujilla ei ollut merkitystä häiriöiden pysyvyyden tai uusiutuvuuden kannalta, mutta neuropsykologisissa tutkimuksissa paremmin suoriutuneilla oli parempi koulutustaso pitkäaikaisseurannassa.

Tulokset osoittavat, että nuoret aikuiset hakevat apua masennus- ja ahdistuneisuushäiriöihin aiempaa useammin, mutta hoidon asianmukaisuudessa on edelleen puutteita. Uusiutumistaipumuksesta huolimatta näiden häiriöiden ennuste on suhteellisen suotuisa, koska yli kolme neljännestä elämänaikaisen diagnoosin saaneista nuorista aikuisista oli toipunut 6–8 vuoden seurannan jälkeen. Häiriöillä oli kuitenkin vaikutusta sairastuneiden koulutustasoon pitkällä tähtäimellä. Jatkossa tulisi perehtyä ja puuttua syihin, jotka estävät asianmukaisen hoidon toteutumisen terveydenhuollossa. Olisi myös tärkeää tehdä sellaisia koulutuspoliittisia ratkaisuja, jotka tukevat myös mielenterveyden häiriöistä kärsivien koulutuksen jatkuvuutta kuntoutumisen aikana ja sen jälkeen.

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Kasteenpohja T, Marttunen M, Aalto-Setälä T, Perälä J, Saarni SI, Suvisaari J: Treatment received and treatment adequacy of depressive disorders among young adults in Finland. BMC Psychiatry Mar 2015;15(1):427.

II Kasteenpohja T, Marttunen M, Aalto-Setälä T, Perälä J, Saarni SI, Suvisaari J: Treatment adequacy of anxiety disorders among young adults in Finland. BMC Psychiatry 2016 Mar 15;16(1):63.

III Kasteenpohja T, Marttunen M, Aalto-Setälä T, Perälä J, Saarni SI, Suvisaari J: Outcome of depressive and anxiety disorders among young adults: Results from the Longitudinal Finnish Health 2011 Study. Nord J Psychiatry. 2018 Apr;72(3):205-213.

IV Kasteenpohja T, Marttunen M, Castaneda AE, Aalto-Setälä T, Perälä J, Saarni SI, Suvisaari J: Cognitive functioning as a predictor of outcome for depressive and anxiety disorders among young adults in the general population. Submitted for publication.

The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

ACTH	Corticotropin
BDNF	Brain-derived neurotrophic factor
CAGE	Cutdown, Annoyed, Guilty, Eye-opener questionnaire
CIDI-SF	Composite International Diagnostic Interview-Short form
COMT	Catechol-O-methyltransferase
CRF	Corticotropin-releasing factor
CVLT	The California Verbal Learning Test
DAX	The study group consisting of young adults of MEAF study with a diagnosis of depressive and/or anxiety disorder at baseline
DD	Dysthymic disorder
DSM-III-R	The Diagnostic and Statistical Manual of Mental Disorders, third edition-Revised
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECA	The Baltimore Epidemiologic Catchment Area
ECT	Electroconvulsive therapy
EDSP	The Early Developmental Stages of Psychopathology
ESEMeD	The European Study of the Epidemiology of Mental Disorders
FINHCS	The Finnish Health Care Survey
GAD	Generalized anxiety disorder
GABA	Gamma-aminobutyric acid
GHQ-12	General Health Questionnaire
HARP	Harvard/Brown Anxiety Disorders Research Program
HPA	Hypothalamic-pituitary-adrenal
HRQoL	Health-related quality of life
5-HTT	Serotonin transporter
ICD-10	The International Classification of Diseases, 10th revision
K10	Kessler Psychological Distress Scale
MAO	Monoamine oxidase
M-CIDI	Munich Composite International Diagnostic Interview
MDD	Major depressive disorder
MDE	Major depressive episode
MDQ	Mood Disorder Questionnaire
MEAF	Mental Health in Early Adulthood in Finland
NOS	Not otherwise specified
NCS-R	National Comorbidity Survey Replication
NEMESIS	The Netherlands Mental Health Survey and Incidence Study
NESARC	The National Epidemiologic Survey on Alcohol and Related Conditions

NESDA	The Netherlands Study of Depression and Anxiety
NHDR	The Finnish National Hospital Discharge Register
NMDA	N-methyl-D-aspartate
NSDUH	The National Survey on Drug Use and Health
OCD	Obsessive-compulsive disorder
ODIN	Outcomes of Depression International Network
PD	Panic disorder
PHQ	Patient Health Questionnaire
PSE	Present State Examination
PTSD	Post-traumatic stress disorder
QOL	Quality of life
SCAN	The Schedules for Clinical Assessment in Neuropsychiatry
SCID-I	Structured Clinical Interview for DSM-IV
SNRI	Serotonin and noradrenaline reuptake inhibitor
SCOFF	Sick,Control,One stone,Fat,Food questionnaire
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TMT	Trail Making Test
UM-CIDI	University of Michigan Composite International Diagnostic Interview
US	The United States of America
WAIS-R	Wechsler Adult Intelligence Scale, Revised
WHO	The World Health Organization
WMH	World Mental Health
WMS-R	Wechsler Memory scale, Revised

1 INTRODUCTION

Depressive and anxiety disorders are among the most common mental disorders worldwide. According to the World Mental Health Survey, the lifetime prevalence of anxiety disorders varied from 4.8% in China to 31.0% in the United States, and for mood disorders lifetime prevalence rates ranged from 3.3% in Nigeria to 21.4% in the United States. The age of onset is often early, for some anxiety disorders already in childhood (Kessler et al. 2007). As depressive and anxiety disorders tend to have a chronic or fluctuating course, and recurrence and residual symptoms after formal recovery are common, there may be widespread and long-lasting effects on the lives of affected persons (Beesdo-Baum et al. 2012; Hardeveld et al. 2010; Hardeveld et al. 2013b; Klein et al. 2006; Markkula et al. 2016; Wittchen et al. 2008).

Remission rates of depressive disorders between 60% and 76% have been reported in recent population-based samples in various age groups, whereas remission rates have ranged from 53% to 78% for different anxiety disorders (Agosti 2014; Batelaan et al. 2010a; Essau et al. 2002; Essau 2007; Hendriks et al. 2013; Nay et al. 2013; Rhebergen et al. 2011). Comorbidity of depressive and anxiety disorders is common, as is a transition from one disorder to another (Jacobi et al. 2004; Lamers et al. 2011; Markkula et al. 2016; Nay et al. 2013; Penninx et al. 2011; Scholten et al. 2013).

Clinical features, such as comorbidity, as well as severity and duration of symptoms, have often been associated with the prognosis of depressive and anxiety disorders in previous studies (Beard et al. 2010; Hendriks et al. 2015; Markkula et al. 2016; Penninx et al. 2011). Findings on the prognostic value of gender and age have been mixed (Eaton et al. 2008; Markkula et al. 2016; Nay et al. 2013; Penninx et al. 2011; Scholten et al. 2013), whereas some sociodemographic factors, such as lower education, not being married and unemployment, have been related to a poor prognosis of these disorders in some studies (Batelaan et al. 2010a; Colman et al. 2007; van Beljouw et al. 2010).

In many population-based studies, there has been no association between treatment and outcome of depressive and anxiety disorders (Bruce et al. 2005; Dowrick et al. 2011; Hardeveld et al. 2013a), or prognoses have been even worse for those with more intensive treatment (Perkonigg et al. 2005; Spijker et al. 2001a; Spijker et al. 2001b; Ten Have et al. 2017). The reason may be that those with more severe symptoms seek and receive treatment more often (Bland et al. 1997; Prins et al. 2011b; Verhaak et al. 2009). However, clinical studies have shown that antidepressive treatment is efficient in preventing relapse of depressive and anxiety disorders, and guideline-concordant treatment has also been associated with better outcomes of these disorders (Batelaan et al. 2017; Hepner et al. 2007; Sim et al. 2015).

According to previous studies, mild cognitive impairment is common in depressive and anxiety disorders (Castaneda et al. 2008b). Clinical studies have found cognitive deficits to influence therapeutic response, risk of relapse, function and quality of life, especially in depressive disorders (Gonda et al. 2015). Population-based studies on cognitive functioning as a predictor of outcome of these disorders are scarce. However, Airaksinen et al. found in a general population-based sample that those who fulfilled the criteria for DSM-IV (The Diagnostic and Statistical Manual of Mental Disorders) depression at a three-year follow-up, did not differ in episodic memory performance at baseline from those who were in remission (Airaksinen et al. 2006).

Depressive and anxiety disorders especially cause non-fatal health outcomes such as work role disability and poor quality of life (Alonso et al. 2004a). As these disorders are also common, their societal consequences are considerable. Hence, depressive disorders were among the leading causes of years lived with disability worldwide in 2016 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). Mood disorders were also the most costly disorders of the brain in Europe mainly due to high indirect costs caused by the disability, whereas anxiety disorders ranked in fourth place (Gustavsson et al. 2011). Mental and substance use disorders, especially major depressive disorder, are also significant risk factors for suicide, being responsible for two-thirds of the suicide burden in 2010. Taking this into account raised these disorders from fifth to third leading disease category of global burden of disease in 2010 (Ferrari et al. 2014).

The impact of depressive and anxiety disorders on quality of life is also significant. Dysthymia, generalized anxiety disorder and social phobia were associated with the largest loss of health-related quality of life (HRQoL) at individual level among mental disorders for Finnish Health 2000 participants aged 30 years and over (Saarni et al. 2007). When 29 chronic conditions were examined, anxiety disorders and depressive disorders had the second and third largest negative impact on HRQoL just after Parkinson's disease (Saarni et al. 2006).

Despite the major negative effects of depressive and anxiety disorders at individual and societal level, these disorders are often unrecognized and undertreated (Alonso et al. 2007; Vermani et al. 2011; Wang et al. 2007a). In the WHO Mental Health Survey on treatment of mood, anxiety and substance use disorders, only 11-16% of severe cases had received any treatment in the previous year. Of those who initiated treatment, 11-42% received minimally adequate treatment (Wang et al. 2007a). Median delays in treatment seeking are also long, ranging from 3 to 30 years for anxiety disorders and from 1 to 14 years for mood disorders (Wang et al. 2007b). Another barrier to adequate treatment is dropping out from treatment, which may be a sign of poor functioning of the healthcare system (Young et al. 2000). In the World Mental Health Survey, overall almost a third of those

who had been treated for mental health reasons in the past 12 months had dropped out (Wells et al. 2013).

The incidence of depressive and anxiety disorders peaks in late adolescence and early adulthood, which is a critical life stage for identity formation and socialization in terms of education, professional career and interpersonal relationships (Kessler et al. 2007; Wittchen et al. 1998b). Hence, untreated mental disorders during this age period may be particularly harmful, since they may impair occupational, academic and social functioning (Asselmann et al. 2018; Wittchen et al. 1998b). Therefore, recognition and adequate treatment of depressive and anxiety disorders among young people are especially important.

Nevertheless, studies that focus on depressive and anxiety disorders among young adults are scarce. In the National Comorbidity Survey Replication, a group of young adults aged 18-29 years was investigated where the lifetime prevalence was 15.4% for major depressive episode and 1.7% for dysthymia. Lifetime prevalence of anxiety disorders varied from 1.1% for agoraphobia without panic to 13.6% for social phobia among young adults (Kessler et al. 2005). Another study from the United States found that only about a fifth of depressed college students had received minimally adequate treatment (Eisenberg and Chung 2012).

Likewise, low figures of treatment seeking for depressive disorders have previously been found in Finland among young adults. In a sample of 15-24-year olds from the Finnish Health Care Survey in 1996, only a fifth of those with major depressive episode had sought treatment for depression during the preceding year (Haarasilta et al. 2003). Another study from Finland investigated young urban adults aged 20-24 in 1995 and found a prevalence of 14.9% for twelve-month depressive disorders. Half of those with depression had reported a contact with mental health services, whereas one third had had treatment contacts during the index episode (Aalto-Setälä et al. 2002).

The aims of this thesis were to investigate treatment seeking, treatment adequacy and outcome of depressive and anxiety disorders among young adults in a general population setting. This study is based on the Mental Health in Early Adulthood (MEAF) study, which is a follow-up study of the Health 2000 young adult sample aged 18-29 years old. The results on outcome were based on the follow-up of this sample as a part of the Health 2011 study.

2 REVIEW OF THE LITERATURE

2.1 DIAGNOSTIC CLASSIFICATION OF DEPRESSIVE AND ANXIETY DISORDERS

2.1.1 DEFINITION OF DEPRESSION AND ANXIETY

The word depression may refer to a short-term depressive affect, which is considered as a normal reaction to different life events involving loss or disappointment. Depressive mood is understood to be a persistent emotion, which together with other symptoms may develop into a depressive disorder (Isometsä 2014b).

Anxiety is considered as a feeling of restlessness or tension related to anticipation of future threat, when actual danger is not present, whereas fear is the emotional response to real threat, accompanied by autonomic arousal necessary for fight or flight. When other symptoms, such as avoidance, occur together with persistent, excessive, debilitating fear or anxiety, an anxiety disorder may be present. (APA 2013; Isometsä 2014a)

Knowledge of the aetiology and pathogenesis of mental disorders is still incomplete. Therefore, a diagnostic classification of these disorders is based on operational diagnostic criteria, which are descriptions of manifest signs and symptoms, their duration and associated impairment or distress. In Finland, the International Classification of Diseases, 10th revision (ICD-10), is used for diagnosing mental disorders in clinical work (WHO 1993). A new version, International Classfication of Diseases, 11th revision (ICD-11), was released by WHO in June 2018 (WHO 2018), but is not yet in use in Finland. Another current diagnostic system, the Diagnostic and Statistical Manual of Mental Disorders, fourth and fifth editions (DSM-IV and DSM-5), is typically used in research processes (APA 2000a; APA 2013). The diagnoses of depressive and anxiety disorders in the studies of this thesis are based on DSM-IV diagnostic classification, which was in use when the data of this study was collected. DSM-V was published in 2013.

2.1.2 DIAGNOSTIC CLASSIFICATION OF DEPRESSIVE DISORDERS

2.1.2.1 DSM-IV

Major depressive disorder

According to DSM-IV diagnostic classification, the diagnosis of major depressive episode (MDE) requires the presence of five of the following symptoms during the same 2-week period: depressed mood; loss of interest

or pleasure; significant weight loss or weight gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate or recurrent thoughts of death or suicide. At least one of two main symptoms, depressed mood or loss of interest or pleasure, have to be present. Furthermore, the symptoms have to be present most of the day, nearly every day. (APA 2000a)

For a diagnosis of MDE, symptoms have to cause clinically significant distress or impairment in social, occupational or other important areas of functioning, and must not be due to substance use or a general medical condition. In addition, mixed episodes including manic features should be excluded. Bereavement is also an exclusion criterion, unless the symptoms persist for longer than 2 months after the loss of a loved one or involve marked functional impairment, worthlessness, suicidal ideation or psychomotor retardation. (APA 2000a)

Establishing a diagnosis of major depressive disorder (MDD, 296.xx) requires the presence of a single (Single episode) or two or more (Recurrent) major depressive episodes. Manic, mixed and hypomanic episodes must be excluded, unless they are due to substance use or general medical condition. Symptoms must not either be related to schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder nor psychotic disorder not otherwise specified. (APA 2000a)

MDD can be classified as mild, moderate, severe without psychotic features or psychotic with mood-congruent or mood-incongruent psychotic features. Specifiers such as with catatonic features, melancholic, atypical, post-partum onset, seasonal pattern and with or without inter-episode recovery may be used. (APA 2000a)

Dysthymic disorder

The main diagnostic criterion of dysthymic disorder (DD, 300.4) is depressed mood for most of the day, for more days than not, for at least 2 years. Additionally, the presence of at least two of the following is required: poor appetite or overeating; insomnia or hypersomnia; low energy; low self-esteem; poor concentration or indecisiveness or hopelessness. (APA 2000a)

For establishing the diagnosis, symptom-free periods must not last more than two months during the period of disturbance, and MDD must not be present during the first two years of the disturbance. Clinically significant distress or impairment in important areas of functioning is also required. Exclusion criteria include manic, mixed and hypomanic episodes, a cyclothymic disorder, a chronic psychotic disorder and symptoms being caused by substance use or a general medical condition. (APA 2000a)

Depressive disorder not otherwise specified

Depressive disorder not otherwise specified (311) includes a range of depressive disorders which do not fulfill the criteria for MDD or DD.

Premenstrual dysphoric disorder is characterized by depressed mood, anxiety, affective lability and decreased interest during the last weeks of the luteal phase of the menstrual cycle. Minor depressive disorder refers to episodes lasting two weeks and characterized by 2-4 depressive symptoms. Recurrent depressive disorder is characterized by brief episodes of recurrent depressive symptoms lasting at least two days but less than two weeks and meeting full criteria of MDD. Mixed anxiety-depressive disorder refers to a syndrome where dysphoric mood lasts at least one month, and at least four symptoms related to MDD, DD, panic disorder or generalized anxiety disorder are required. Post-psychotic depressive disorder of schizophrenia includes depressive episodes, which occur during the residual phase of schizophrenia. (APA 2000a)

2.1.2.2 Differences between DSM-IV and DSM-5

The core criteria of major depressive disorder have remained unchanged during transition from DSM-IV to DSM-5. The main difference is omission of bereavement from exclusion criteria in DSM-5. The reason for this change is that bereavement has many similar features in risk factors and course as MDD, and responds to the same types of treatment. Additionally, the 2-month time period does not correspond to the actual duration of the grieving. Thus, DSM-5 emphasizes clinical judgement in distinguishing grief from MDD. (APA 2000a; APA 2013; Zisook et al. 2012)

In DSM-5, the formerly dysthymic disorder is called persistent depressive disorder, and it includes chronic major depressive disorder as well as previous dysthymia. Thus, unlike dysthymia in DSM-IV, this diagnosis allows the presence of MDD during the 2-year disorder period. (APA 2000a; APA 2013)

What was referred to as depressive disorder not otherwise specified in DSM-IV, is called other specified depressive disorder in DSM-5. This diagnosis covers, for example, such disorders as recurrent brief depression, short-duration depressive episode and depressive episode with insufficient symptoms to meet the criteria for MDD. The diagnosis of other specified depressive disorder is used if the clinician chooses not to specify the reason that the criteria are not met for a specific depressive disorder, for example, because of insufficient information. (APA 2000a; APA 2013)

DSM-5 contains a few new depressive disorders: premenstrual dysphoric disorder, which formerly fell under the category “depressive disorder not otherwise specified”. It has been moved from the Appendix to the main body of DSM-5. A diagnosis of disruptive mood dysregulation disorder for children up to 12 years has been added to the category of depressive disorders because of concerns about the overdiagnosis of bipolar disorder in children with persistent irritability and behavioural dysfunction. (APA 2000a; APA 2013)

Finally, two new specifiers are available for depressive disorders. A specifier “with mixed features” now enables the coexistence of at least three

manic symptoms within depressive disorders. Another new specifier "with anxious distress" makes it possible to define the level of anxiousness during depressive episodes. (APA 2000a; APA 2013)

2.1.2.3 Differences between DSM-IV and ICD-10

ICD-10 diagnostic manual separates single (F32) and recurrent episodes (F33) of depressive disorder into distinct diagnoses. A diagnosis of recurrent depression in ICD-10 requires a two-month period without any mood-related symptoms between depressive episodes, whereas DSM-IV demands two months in which full criteria of major depressive episode have not been met. (APA 2000a; WHO 1993)

The time criterion of two weeks for depressive episode is similar in both diagnostic classifications. However, ICD-10 names three core symptoms, depressed mood, loss of energy and loss of interest, of which two, and in severe cases three, are required for a diagnosis. ICD-10 lists altogether 10 symptoms separating loss of self-esteem and pessimistic thoughts about the future into distinct entities. On the other hand, psychomotor agitation or retardation is not mentioned. The severity of episodes is defined on the basis of the number of symptoms: a mild episode requires altogether four symptoms, moderate six symptoms and severe episode seven symptoms. A diagnosis of a severe, psychotic depressive disorder excludes bizarre delusions and hallucinations, which lead to a diagnosis of schizoaffective disorder in ICD-10, but in DSM-IV are categorized as mood-incongruent psychotic features. (APA 2000a; WHO 1993)

In ICD-10, dysthymic disorder (F34.1) is defined as a disorder where mild depressive episodes, of which none or very few fulfills the criteria of mild depressive episode, recur during a two-year time period, and symptom-free periods do not last more than a few weeks. Thus, dysthymic disorder in ICD-10 allows MDD to be present during the disorder period, and dysthymic disorder may follow an episode of MDD without a symptom-free period, in contrast to DSM-IV. (APA 2000a; WHO 1993)

In addition to depressed mood, ICD-10 lists 11 symptoms, of which at least three must be present, whereas DSM-IV requires 2 of 6 symptoms. The possible symptoms are: reduction in energy; insomnia; loss of self-confidence; poor concentration; tearfulness; loss of interest in sex and other pleasurable activities; hopelessness; perceived inability to cope with everyday responsibilities; pessimistic attitude toward the future or worrying about the past; social withdrawal and being less talkative than usual. (APA 2000a; WHO 1993)

2.1.3 DIAGNOSTIC CLASSIFICATION OF ANXIETY DISORDERS

2.1.3.1 DSM-IV

Panic disorder and agoraphobia

DSM-IV defines panic attack as a discrete period of intense fear or discomfort, in which at least four of the listed symptoms develop suddenly reaching a peak within 10 minutes. The possible symptoms are: palpitations; sweating; trembling; sensations of shortness of breath; feeling of choking, discomfort in chest; nausea or abdominal distress; feeling dizzy or faint; derealization or depersonalization; fear of losing control; paraesthesias and chills or hot flushes. (APA 2000a)

Agoraphobia is defined as anxiety about being in places or situations from which escape could be difficult or embarrassing, or in which help may not be available if having panic-like symptoms. These situations are avoided or faced with marked distress or anxiety about having a panic attack. The third criterion excludes such mental disorders as social phobia, specific phobia, obsessive-compulsive disorder, post-traumatic stress disorder and separation anxiety disorder as a reason for anxiety or phobic avoidance. If agoraphobia related to fear of panic-like symptoms is present, but criteria for panic disorder have not been met, a diagnosis of agoraphobia without history of panic disorder (300.22) can be established. Exclusion criteria involve direct physiological effects of a substance or a general medical condition. In the case of general medical condition, the fear must be clearly in excess of that which is usually associated with that condition. (APA 2000a)

A diagnosis of panic disorder (PD) without agoraphobia (300.01) demands the presence of recurrent unexpected panic attacks. In addition, at least one of the attacks has to have been followed by at least 1 month of persistent concern about having additional attacks, worry about the implications of the attack or its consequences or a significant change in behaviour related to the attacks. Agoraphobia must not be present. The diagnosis of panic disorder is not established if the symptoms are a consequence of physiological effects of a substance or a general medical condition, or are better explained by such disorders as social phobia, specific phobia, obsessive-compulsive disorder, post-traumatic stress disorder or separation anxiety disorder. The diagnostic criteria of panic disorder with agoraphobia (300.21) are otherwise the same, but agoraphobia must be present. (APA 2000a)

Specific phobia

The main symptom of specific phobia (300.29) is excessive or unreasonable fear cued by the presence or anticipation of a specific object or situation. Different subtypes are classified according to the focus of fear or avoidance, which may be animal type, natural environment type, blood-injection-injury type, situational type or other type. Exposure to the phobic situation almost

invariably provokes an immediate anxiety response, which may emerge as a panic attack. This leads to intense anxiety or distress in a phobic situation, or complete avoidance of phobic stimulus. To differentiate this disorder, for example, from delusional disorder, it is demanded for the diagnosis that the adult person recognizes the fear to be excessive or unreasonable. The establishment of this diagnosis also demands that the avoidance, anxious anticipation or distress interferes significantly with the person's social or occupational functioning or daily performance. The exclusion criterion contains other mental disorders, like obsessive-compulsive disorder, social phobia or panic disorder. For persons under 18 years old, symptoms must last at least 6 months to establish a diagnosis. (APA 2000a)

Social phobia

According to DSM-IV, social phobia (300.23) is a disorder where excessive or unreasonable fear or anxiety is provoked in one or more social situations, where humiliation or embarrassment because of one's action or anxiety symptoms is possible. Exposure to the feared social situation almost invariably provokes anxiety, possibly emerging as a panic attack, which causes avoidance of these situations or enduring them with marked distress. As in other phobias, for establishing a diagnosis the adult person must recognize that the fear is excessive or unreasonable, and the symptoms must interfere significantly with the person's normal life. The time criterion of 6 months for individuals under 18 years old is also present. Direct physiological effects of a substance or a general medical condition, and other mental disorders, must be excluded, unless the fear of the social situation is unrelated to these other conditions. Social phobia can be specified as generalized, if the fears are related to most social situations. (APA 2000a)

Obsessive–compulsive disorder

In obsessive-compulsive disorder (OCD, 300.3), recurrent obsessions or compulsions are present to the extent that they cause significant distress or impairment or take up more than 1 hour a day. Obsessions are defined as recurrent thoughts, impulses or images that are experienced as intrusive and inappropriate and are not just excessive worries about real life problems. The person recognizes them as a product of his or her own mind and attempts to ignore or suppress them. Compulsions are repetitive behaviours or mental acts performed in response to an obsession or according to rigid rules. They are aimed to prevent or reduce distress or prevent some dreaded event or situation, but are clearly excessive or not realistic for that purpose. The adult person with this disorder recognizes that the obsessions and compulsions are excessive or unreasonable. However, if this does not happen for most of the time during the current episode, the specifier "with poor insight" can be used. For establishing a diagnosis, the content of obsessions or compulsions must not be restricted to another Axis I disorder, and symptoms must not be

due to direct physiological effects of a substance or a general medical condition. (APA 2000a)

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD, 309.81) may emerge when the person has experienced, witnessed or was confronted with an event that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others, and the person's initial response involved intense fear, helplessness or horror. In the case of this disorder, the traumatic event is persistently re-experienced by recurrent, intrusive and distressing recollections of the event, recurrent distressing dreams of the event, acting or feeling as if the traumatic event were recurring or intense psychological distress or physiological reactivity at exposure to internal or external cues of the traumatic event. Diagnostic criteria also require at least 3 symptoms indicating persistent avoidance of stimuli from the trauma and numbing of general responsiveness: efforts to avoid thoughts, feelings or conversations associated with the trauma; efforts to avoid activities, places or people evoking recollection of the trauma; amnesia of an important aspect of the traumatic event; markedly diminished interest or participation in signicant activities; feeling of detachment or estrangement from others; reduced ability to feel emotions and sense of a foreshortened future. At least two symptoms of increased arousal should also be present: difficulty falling or staying asleep; irritability or outbursts of anger; difficulties in concentration; hypervigilance or exaggerated startle response. For establishing a diagnosis, symptoms have to cause clinically significant distress or impairment in important areas of functioning and last at least 1 month. The disorder may be specified as acute, if symptom duration is less than 3 months, chronic, if duration is at least 3 months, and with delayed onset, if onset of symptoms is at least 6 months after the stressor. (APA 2000a)

Generalized anxiety disorder

According to DSM-IV, generalized anxiety disorder (GAD, 300.02) is characterized by excessive anxiety and worry which the person finds difficult to control, occurring more days than not for at least 6 months and concerning several events or activities. At least three of the following additional symptoms have to be present: restlessness; being easily fatigued; difficulties in concentration; irritability; muscle tension or sleep disturbance. The anxiety, worry or physical symptoms have to cause clinically significant distress or impairment in daily functioning. The focus of the anxiety or worry must not be confined to features of another Axis I disorder, and the disorder does not occur exclusively during a mood disorder, psychotic disorder or a pervasive developmental disorder. Diagnostic criteria also exclude symptoms caused by direct physiological effects of a substance or a general medical condition. (APA 2000a)

Anxiety disorder not otherwise specified
The diagnosis of anxiety disorder not otherwise specified (NOS) (300.0) is established if a disorder does not meet criteria for any specific anxiety disorder, adjustment disorder with anxiety or adjustment disorder with mixed anxiety and depressed mood. (APA 2000a)

Other anxiety disorders
The category of other anxiety disorders in the DSM-IV also includes such disorders as acute stress disorder (308.3), anxiety disorder due to a general medical condition (293.89) and substance-induced anxiety disorder, which are not referenced in the studies of this thesis. (APA 2000a)

2.1.3.2 Differences between DSM-IV and DSM-5

There are some marked differences related to anxiety disorders between DSM-IV and DSM-5. First, obsessive-compulsive disorder is no longer under the section of anxiety disorders, but is included in a new category "Obsessive-Compulsive and Related Disorders". Post-traumatic stress disorder and acute stress disorder are also removed from anxiety disorders, and are now in another new category of "Trauma- and stressor-related disorders". On the other hand, separation anxiety disorder and selective mutism, formerly included in the section "Disorders Usually First Diagnosed in Infancy", have been included in the category of anxiety disorders in DSM-5. (APA 2000a; APA 2013)

In DSM-5, panic disorder and agoraphobia are two different disorders, which may appear together or separately. This change has emerged from the finding that many individuals with agoraphobia do not experience panic attacks. The diagnostic criteria of agoraphobia are very similar to descriptors of agoraphobia in DSM-IV, but anxiety in at least two agoraphobic situations is demanded for the diagnosis. Additionally, the fear has to be out of proportion to the actual danger of the agoraphobic situation, cause clinically significant distress or impairment in functioning and last at least 6 months. For panic disorder, diagnostic criteria are mainly the same as in DSM-IV. A new addition is that panic attack can be used as a specifier to all DSM-5 disorders as a marker for severity of a disorder. (APA 2000a; APA 2013)

For social anxiety disorder, a change has been made to specifier "generalized", which has been replaced with a specifier "performance only". It has been presented that fear of only performance situations would present a different type of social anxiety disorder in many aspects. The time criterion of 6-month duration has been extended to all ages in social anxiety disorder as well as specific phobias. The requirement that individuals over 18 years of age recognize their anxiety to be excessive has been deleted from criteria regarding all phobias. Instead, the anxiety has to be out of proportion to the actual danger posed by the feared stimulus and the sociocultural context. (APA 2000a; APA 2013)

2.1.3.3 Differences between DSM-IV and ICD-10

ICD-10 classifies anxiety disorders under the main category which includes neurotic, stress-related as well as somatoform disorders. The subsection "Phobic anxiety disorders" (F40) includes agoraphobia, social phobias, specific (isolated) phobias, other phobic anxiety disorders and unspecified phobic anxiety disorders. The subsection "Other anxiety disorders" (F41) comprises panic disorder, generalized anxiety disorder, mixed anxiety and depressive disorder, other mixed anxiety disorder, other specified anxiety disorder and unspecified anxiety disorder. Obsessive-compulsive disorder (F42) is a category of its own, including obsessive-compulsive disorder with predominantly obsessional thoughts and ruminations, with predominantly compulsive acts, with mixed obsessional thoughts and acts, other obsessive-compulsive disorder and unspecified obsessive-compulsive disorder. Post-traumatic stress disorder goes under the section "Reaction to severe stress, and adjustment disorders" (F43). (WHO 1993)

In ICD-10, panic disorder (F41.0) and agoraphobia (F40.0) are two separate disorders, not linked to each other as in DSM-IV. For panic attack, the ICD-10 diagnostic criteria are almost the same as those in DSM-IV, but they include 1 additional symptom, which is dry mouth. ICD-10 also requires that at least one of the symptoms has to be palpitations, sweating, trembling or dry mouth. On the other hand, ICD-10 does not demand persistent concern about additional attacks or their consequences, or a significant change in behaviour related to the attacks. In ICD-10, panic disorders are divided into mild, moderate, severe and non-specified types. (APA 2000a; WHO 1993)

According to ICD-10, diagnosis of agoraphobia requires fear or avoidance of at least 2 of four specified situations, which are crowds, public places, travelling alone or travelling away from home. Additionally, ICD-10 demands that at least two symptoms of panic attack have been present simultaneously in at least one situation, and at least one symptom is palpitations, sweating, trembling or dry mouth. There is also a criterion that symptoms should be restricted to the feared situations or contemplation of them. In contrast, DSM-IV does not demand specific feared situations or specific types of anxiety symptoms for the diagnosis of agoraphobia. (APA 2000a; WHO 1993)

The ICD-10 diagnostic criteria for social phobia (40.1) defines anxiety symptoms more precisely than DSM-IV. ICD-10 requires that at least two anxiety symptoms occurring in panic attacks have been present in the social situation, and additionally one of the following symptoms has emerged: blushing or shaking; fear of vomiting or urgency or fear of micturition or defecation. For both social phobia and specific phobias (F40.2), ICD-10 diagnostic criteria demand that anxiety symptoms have to be restricted to, or predominate in, the feared situations or contemplation of these situations, while DSM-IV does not restrict the situations where anxiety can occur. ICD-10 does not include a time criterion of 6 months even for those less than 18

years old for these disorders. Nor does ICD-10 demand that symptoms interfere significantly with the person's functioning. (APA 2000a; WHO 1993)

The main difference between DSM-IV and ICD-10 concerning diagnostic criteria of obsessive-compulsive disorder is a distinction between obsessions and compulsions. According to ICD-10, obsessions are thoughts, ideas or images and compulsions are acts, though including such mental acts as counting. In contrast, according to DSM-IV, obsessions are thoughts, images or impulses which cause anxiety or distress, and compulsions are repetitive behaviours or mental acts performed to prevent or reduce distress. Therefore, compulsions may also be cognitive by nature, and obsessions are not only cognitive events. Thus, obsessions and compulsions are distinctive by their function (Leckman et al. 2010). ICD-10 also classifies these disorders as obsessive-compulsive disorder with predominantly obsessional thoughts and ruminations (F42.0), with predominantly compulsive acts (F42.1) and with mixed obsessional thoughts and acts (F42.2). Additionally, for establishing a diagnosis ICD-10 demands a minimum duration of two weeks for symptoms, which is not required in DSM-IV (APA 2000a; WHO 1993).

For the diagnosis of post-traumatic stress disorder (F43.1), the definition of exposure is not as precise in ICD-10 as it is in DSM-IV. In ICD-10 it is defined as an event "of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone". ICD-10 does not either specify different symptoms which relate to avoiding stimuli associated to trauma, nor does it demand persistent symptoms of increased arousal if an inability to recall important aspects of trauma is present. In addition, there is not a minimum duration of 1 month for symptoms in ICD-10, but symptoms have to appear within 6 months after a traumatic event. Again, clinically significant distress or impairment is not required in ICD-10 for establishing the diagnosis of post-traumatic stress disorder. (APA 2000a; WHO 1993)

ICD-10 diagnostic criteria for generalized anxiety disorder (F41.1) specifies 22 symptoms in categories of autonomic arousal symptoms; symptoms concerning chest and abdomen; symptoms concerning brain and mind; general symptoms; symptoms of tension and other non-specific symptoms. Establishing a diagnosis demands that four of these symptoms are present, one of them being from the category of autonomic arousal symptoms. DSM-IV requires 3 of 6 symptoms, of which 5 are also included in ICD-10 symptom list. The ICD-10 diagnostic criteria do not demand that symptoms have to cause marked impairment in daily life. (APA 2000a; WHO 1993)

2.2 AETIOLOGY AND PATHOGENESIS OF DEPRESSIVE AND ANXIETY DISORDERS

2.2.1 DEPRESSIVE DISORDERS

The diagnosis of mental disorders is based on symptoms and signs and clinical course of these disorders, suggesting that a disorder is not necessarily a separate entity, but may be the outcome of different pathophysiological pathways (equifinality) (Hasler 2010). In their recent review, Jesulola et al. stated on the aetiology of depression that "environmental stressors and heritable genetic factors acting through immunologic and endocrine responses initiate structural and functional changes in many brain regions, resulting in dysfunctional neurogenesis and neurotransmission which then manifest as a constellation of symptoms which present as depression" (Jesulola et al. 2018).

2.2.1.1 Heredity

According to family, twin and adoption studies, MDD is a familial disorder in which the heritability is 30-40%, greater in women than in men (Sullivan et al. 2000). It has been estimated that men and women share most, but not all genes predisposing to depression (Kendler et al. 2001). The heritability of MDD is lower than the heritability of schizophrenia, autism and bipolar disorder (Bienvenu et al. 2011), which suggests that environmental factors play a greater role in the aetiology of MDD than genetic factors. Accordingly, in contrast to schizophrenia, genome-wide association studies have been able to identify few genome-wide significant loci for MDD (Power et al. 2017), and numerous studies on candidate genes have not been able to prove a role of specific genes in the pathogenesis of MDD. In contrast, several genome-wide significant loci have been identified for depressive symptoms (Turley et al. 2018). Gene-by-environment interactions are likely, meaning that genes modify the effect of environment on susceptibility to depression. On the other hand, environmental experiences may also modify gene function by epigenetic changes in the absence of DNA sequence changes (Chirita et al. 2015). These mechanisms are demonstrated by the study of Caspi et al., where a functional polymorphism region of the serotonin transporter (5-HTT) gene moderated the influence of stressful life events on depression, but the association between genotype and depression not associated with life events was not significant (Caspi et al. 2003). Genes connected to depressive disorders are also associated, for example, to certain personality traits which predispose to depression or internalizing disorders in general (Brainstorm Consortium et al. 2018). Personality traits, such as high neuroticism, low extraversion and low conscientiousness have been related to several internalizing disorders (Kotov et al. 2010).

The serotonin transporter gene is a classic candidate gene for depression. Several other studies have also focused on genes related to functioning of monoamines or other known pathophysiological pathways of depression (Jesulola et al. 2018; López León et al. 2005; Lopez-Leon et al. 2008). New candidate genes have emerged as a result of new aetiological hypotheses about depression. One of the genes gaining further attention is brain-derived neurotrophic factor, a protein having neuroprotective response to stress (Levinson 2006).

2.2.1.2 Environmental risk factors

Previous studies have shown the connection between the stress system and depression, and depression has been suggested to be a possible outcome of dysregulation of the stress response system. Stress-related structural changes in the prefrontal cortex, amygdala, hippocampus and nucleus accumbens have also been seen to participate in the development of depression. As acute and chronic life events seem to influence the onset and recurrence of MDD, there is also evidence of the effect of positive life events as protection against the development of depression. (Jesulola et al. 2018)

Many childhood adversities, such as sexual and physical abuse (Chen et al. 2014; Stegenga et al. 2013), exposure to bullying (Bowes et al. 2015; Sourander et al. 2016) and low parental education (Park et al. 2013; Ritsher et al. 2001) have often been related to depression. However, stressful life events and low socioeconomic position in adulthood may also be involved in the development of depression (Lehtinen et al. 2005), since unemployment, low education, financial strain and low income have been associated with the risk of depression (Stegenga et al. 2013; Wang et al. 2010).

Social capital dimensions of trust and reciprocity as well as social participation have been seen to contribute to psychological well-being (Nieminen et al. 2010). Therefore, they can be seen as protective factors against mental disorders, whereas low social participation, low social support, problems with neighbourhood and being separated have been shown to increase the risk of depression (Kivelä et al. 1996; Stegenga et al. 2013).

Health behaviours, such as smoking (Chaiton et al. 2009), alcohol and cannabis use (Boden and Fergusson 2011; Lev-Ran et al. 2014) and being overweight (Luppino et al. 2010) have been associated with depression. On the other hand, leisure time physical activity (Wiles et al. 2007) and some dietary patterns (Martinez-Gonzalez and Sanchez-Villegas 2016) have been shown to be protective factors. Mediterranean-type diets have been especially associated with a lower incidence of depression, but current evidence is still limited (Martinez-Gonzalez and Sanchez-Villegas 2016; Ruusunen et al. 2014).

2.2.1.3 Neurotransmission

The “monoamine hypothesis” of depression refers to reduced availability of monoamine neurotransmitters; serotonin, dopamine and noradrenalin, resulting in decreased neurotransmission and impaired cognitive functioning which may lead to depression. Located in the midbrain and brainstem nuclei and projecting to large areas of the brain, monoaminergic systems are involved in the regulation of many brain functions, such as mood, attention, reward processing, sleep, appetite and cognition. Alterations in monoaminergic systems have been linked to a broad range of symptoms in depression: behavioural and somatic functions, such as sleep, sex, pain response, body temperature and circadian rhythm are associated with cerebral serotonin levels. Impaired motivation, concentration and aggression have been found to be associated with dopamine abnormalities. Low noradrenaline levels mediate symptoms related to sex, appetite, aggression, concentration, interest and motivation. (Hasler 2010; Jesulola et al. 2018)

According to the monoamine hypothesis, functional deficiency of monoamine transmitters is due to increased activity of monoamine oxidase enzyme participating in the metabolism of monoamines. This leads to a reduction in the availability of monoamines and decreased neurotransmission. In depressed individuals, increased monoamine oxidase activity has actually been detected. Monoamine oxidase enzyme is also a target of monoamine oxidase inhibitors that induce increased availability of monoamines in presynaptic neurons. These compounds have been used widely as antidepressant medication. (Hasler 2010; Jesulola et al. 2018)

The reason for functional deficiency of monoamines may also be a decreased transport protein function, which is a target of selective serotonin reuptake inhibitor (SSRI) and dual-acting serotonin-norepinephrine inhibitor medication (Jesulola et al. 2018; Mann 2005). Other explanations for monoamine deficiency include a hypothesis concerning a depression-related stress response, which may lead to a decrease of serotonin production (Strawbridge et al. 2017) and abnormalities in monoamine receptor functioning. These hypotheses are supported by findings of impaired protein transporter function and changes in the number and affinity of monoamine receptors in depression (Kaufman et al. 2016; Owens and Nemeroff 1994).

Though almost all antidepressants work through monoamine systems, mainly serotonin and noradrenalin, possible resistance to them and delayed action supports the idea that monoamine deficiency is more likely a contributor to the pathogenesis of depression (Hasler 2010). This is also confirmed by monoamine depletion studies, which have failed to demonstrate a causal relation between serotonin, noradrenalin and depression (Ruhe et al. 2007).

There is some evidence on the contribution of other neurotransmitters, such as glutamate and gamma-aminobutyric acid (GABA), in the pathogenesis of depression (Hasler 2010). Glutamate is the major excitatory neurotransmitter broadly affecting the central nervous system. Interest in

glutamate has increased after the discovery that a single dose of the glutamate N-methyl–D-aspartate (NMDA) receptor antagonist ketamine has a rapid and potent antidepressant effect even in treatment-resistant MDD patients (Niciu et al. 2014). The mood stabilizer lamotrigine, an inhibitor of glutamate release, also has antidepressive qualities. The role of glutamate in the pathogenesis of depression is supported by post-mortem and neuroimaging studies, which have found alterations in the glutamate system of depressed subjects (Hasler 2010). GABA is a major inhibitory neurotransmitter widely involved in the modulation of cognitive and behavioural processes of the brain, especially anxiety and stress responses. Neuroimaging studies have shown reduction in total concentrations of GABA in the prefrontal and occipital cortex in depression (Hasler et al. 2007).

Electroconvulsive therapy (ECT) treatment has been found to affect transmission of almost all the major neurotransmitters in the brain at multiple levels (Singh and Kar 2017).

2.2.1.4 Structural and functional changes in the brain

There is significant heterogeneity in the findings of neuroimaging studies concerning depression. However, the most robust evidence is found in abnormalities of the prefrontal cortex and subgenual cingulate cortex in some subjects with MDD: areas seen to be involved in attention, and emotion experience and processing (Ressler and Mayberg 2007). Previous studies have found large volume reductions in frontal regions, particularly in the anterior cingulate and orbitofrontal cortex, and smaller reductions in the prefrontal cortex. Moderate volume reductions were seen in the hippocampus, the putamen and caudate nucleus (Koolschijn et al. 2009; Zhang et al. 2018). In functional imaging studies, hypoactivity was seen in the frontal and temporal cortex, insula and cerebellum, with increased activity in treatment. Opposite changes were found in subcortical and limbic regions. The anterior cingulate cortex showed differences in response activation with positive stimuli and a decrease in activity with SSRI treatment (Fitzgerald et al. 2008; Zhang et al. 2018).

Neuromodulation treatments aim to target those areas involved in disrupted emotion circuits: transcranial magnetic stimulation of the dorsolateral prefrontal cortex has been effective treatment for some depressive patients (aan het Rot et al. 2009). Chronic deep brain stimulation, often targeted to the subgenual cingulate cortex, has been associated with clinical benefits especially in patients with treatment-resistant depression (Mosley et al. 2015). Increases in hippocampal and amygdala volumes have been reported with electroconvulsive therapy. Symptom improvement has been suggested to be related to these changes in the amygdala, although with an increase in functional connectivity rather than volume changes in hippocampus. Overall, ECT-induced volume changes have been more pronounced in areas with greater connection to prefrontal cortex and other

limbic structures which are involved in regulation of mood (Singh and Kar 2017).

2.2.1.5 HPA axis and other endocrine factors

One consistent finding in major depression is hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Its activation is initiated by perception of psychological stress by cortical brain regions, which induces secretion of corticotropin-releasing factor (CRF) from the hypothalamus. This activates the secretion of pituitary corticotropin (ACTH), which in turn stimulates the adrenal cortex to secrete cortisol. Cortisol interacts with its receptors, which in the HPA axis causes feedback inhibition on CRF from the hypothalamus and ACTH from pituitary (Pariante and Lightman 2008). Previous studies have shown that depressed patients have hypersecretion of CRF and cortisol (Jesulola et al. 2018). This increased activity of the HPA axis seems to be associated with impaired cortisol-mediated feedback inhibition. This is supported by studies showing that in contrast to healthy controls, an oral dose of synthetic glucocorticoid, dexamethasone, does not suppress the HPA axis in the majority of depressed patients (Pariante and Lightman 2008; Vreeburg et al. 2009).

More evidence for the role of CRF in the pathogenesis of depression has been obtained from studies which have found elevated cerebrospinal fluid and brain CRF concentrations and decreased CRF receptor density in depressed subjects (Austin et al. 2003; Nemeroff et al. 1984; Nemeroff et al. 1988). CRF is also known to produce physiological and behavioural symptoms seen in depression, such as decreased appetite, disrupted sleep, decreased libido and psychomotor alterations (Jesulola et al. 2018). On the other hand, concentrations of cerebrospinal fluid CRF have been reduced when depressed subjects have been successfully treated with ECT or SSRI, fluoxetine (Austin et al. 2003; De Bellis et al. 1993; Nemeroff et al. 1991). Moreover, hypercortisolemia is known to inhibit neurogenesis in the hippocampus and cause structural and functional changes in the prefrontal cortex, hippocampus and amygdala, which are areas linked to symptoms of depression (Jesulola et al. 2018). Treatment with ECT has been seen to reduce this cortisol-induced inhibition of neuroplasticity (Singh and Kar 2017).

All subjects with depressive disorders have not shown evidence of a dysfunctional HPA axis. Nevertheless, higher cortisol levels have been linked with the intensity and severity of depression and with early relapse in improved patients (Gillespie and Nemeroff 2005; Jesulola et al. 2018). It has also been found that altered stress hormone secretion was most significant in depressed subjects with childhood trauma, emphasizing the link between stress and depression (Heim et al. 2008).

It has been suggested that thyroid hormones may also be linked to the pathogenesis of depression. Thyroid function abnormalities are known to

cause depression-like symptoms, such as weight loss, sleep disturbance and psychomotor agitation. It has been suggested that thyroid hormone dysfunction contributes to the pathogenesis of depression through serotonergic and/or adrenergic systems. There has also been discussion on the role of pituitary growth hormone in the pathogenesis of depression. (Jesulola et al. 2018)

2.2.1.6 Immunologic factors

Recently, the role of inflammation in the pathogenesis of depression has attracted interest because of studies which have found association between chronic stress and changes in immune function (Dantzer et al. 2008). Cytokines, such as interferons, interleukins and tumour necrosis factor, and C-reactive protein are inflammatory mediators, which defend an organism against foreign antigens and regulate other immune cells. In previous studies, increased levels of cytokines have been found in depressed subjects. It has also been noticed that specific cytokines induce symptoms similar to depression. A few studies show that pro-inflammatory cytokines interfere with brain neuroplasticity and monoamine activity as well as activate the HPA axis by increasing glucocorticoid receptor resistance, acting as potential link for stress-induced depression. Some studies have demonstrated that antidepressant therapy suppresses the activation of inflammatory response (Dantzer et al. 2008; Singh and Kar 2017), and ECT treatment has been seen to decrease the levels of inflammatory mediators (Singh and Kar 2017). Nevertheless, inconsistencies in results suggest that the association between depression and inflammatory factors is more complex. One explanation for the mechanism is “sickness behaviour”, which is a result of an activation of the inflammatory response system. It is mediated by pro-inflammatory cytokines acting on multiple receptors in the brain and inducing depression-like symptoms, such as fatigue, anhedonia, psychomotor retardation and cognitive impairment. These symptoms may be beneficial to affected individuals for saving energy and coping with illness, but in severe cases may develop into a depressive disorder (Dantzer et al. 2008).

2.2.1.7 Neurogenesis

Volume loss of the hippocampus related to the duration of illness has been found in depressed subjects. Speculation on the mechanism of volume loss concern glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors and decreased neurogenesis. Stress-induced hypercortisolemia has been shown to inhibit neurogenesis in the hippocampus. Previous studies have also shown associations between stress-induced depressive symptoms and decreased level of brain-derived neurotrophic factor (BDNF). Additionally, antidepressant and ECT treatment

has been seen to increase the levels of BDNF (Hasler 2010; Jesulola et al. 2018; Singh and Kar 2017). These findings emphasize the possible role of neurotrophic factors and neurogenesis in the pathogenesis of depression.

2.2.1.8 Circadian rhythms

Disturbances of sleep and circadian rhythm are typical symptoms in depressive disorders. On the other hand, manipulation of circadian rhythm, such as sleep deprivation and phase advance treatment, may be beneficial therapies in depression. Thus, circadian abnormalities have been suggested to be involved in the pathogenesis of depressive disorders. This is supported by findings of phase advance of sleep-wake cycle, phase advances in nocturnal cortisol secretion and shortened REM latency in some subjects with MDD. Additionally, antidepressants have been seen to effect circadian rhythms of behaviour, physiology and endocrinology. However, the precise mechanism between circadian abnormalities and depressive disorders is unknown. (Hasler 2010; Partonen 2012)

2.2.2 ANXIETY DISORDERS

As in depressive disorders, anxiety disorders are multifactorial disorders, showing equifinality and also multifinality, where one risk factor may result in various outcomes. (Spence and Rapee 2016)

2.2.2.1 Heredity

For different anxiety disorders, heritability estimates have varied between 13-60% (Aouizerate et al. 2004; Leichsenring and Leweke 2017; Ninan and Dunlop 2005; Roy-Byrne et al. 2006; Spence and Rapee 2016). It is suggested that although these familial associations do not reflect a risk for specific anxiety disorders there is an increased risk for a range of internalizing problems. Genetic factors may contribute to mental health problems, for example, through vulnerable temperament: traits such as behavioural inhibition, shyness, neuroticism and anxiety sensitivity have been associated with anxiety disorders (Leichsenring and Leweke 2017; Mathew and Ho 2006; Morris 2001; Newman et al. 2013; Roy-Byrne et al. 2006; Spence and Rapee 2016; Tseng et al. 2014). For neuroticism, several genome-wide significant loci have been identified in genome-wide association studies (Turley et al. 2018).

Studies on gene candidates in the pathophysiology of anxiety disorders have mostly focused on those genes related to serotonin and dopamine systems. In fact, the serotonin transporter gene polymorphism has been associated with predisposition to anxiety, avoidant behaviour and negative affect in many studies. Associations with different anxiety disorders have also

been found concerning the gene for catechol-O-methyltransferase (COMT), the enzyme responsible for metabolism of dopamine, adrenalin and noradrenalin. (Aouizerate et al. 2004; Mathew and Ho 2006; Ninan and Dunlop 2005; Roy-Byrne et al. 2006; Spence and Rapee 2016)

2.2.2.2 Environmental risk factors

As in depressive disorders, biological factors are intertwined with environmental factors. Even prenatal and neonatal stressors, such as high levels of anxiety and depression during pregnancy, have been seen to cause dysregulation of the HPA axis. This again has been associated with impairments in brain maturation and function that lead to a wide range of behavioural disruptions, such as depressive and anxiety disorders (Schiele and Domschke 2018).

In childhood, external influences may have particularly harmful and long-lasting effects on neurodevelopmental processes. Hence, environmental factors early in life, such as adverse/stressful life events, insecure attachment, parenting styles (overprotection and rejection) and peer victimization have been suggested to play a role in the development of different anxiety disorders (Leichsenring and Leweke 2017; Mathew and Ho 2006; Morris 2001; Newman et al. 2013; Ninan and Dunlop 2005; Roy-Byrne et al. 2006; Spence and Rapee 2016). Even in adulthood, negative life events like illness, loss, separation events, financial problems and threat experiences have been observed to precede anxiety disorder onset (Schiele and Domschke 2018). However, a highly positive environment may serve as a protective factor (Spence and Rapee 2016).

2.2.2.3 Neurotransmission

It has been presented that fear regulation and threat responsiveness are linked to serotonin signalling, for instance, low levels of serotonin in cerebrospinal fluid have been reported. However, it has been uncertain whether serotonin is basically anxiolytic or anxiogenic. The explanation to this controversy may be that there are two major serotonergic systems in the brain: serotonin facilitates inhibitory avoidance in the limbic forebrain (amygdala and frontal cortex), whereas it inhibits one-way escape in the midbrain (dorsal periaqueductal grey matter). It has been suggested that serotonin dysfunction in one or both systems leads to different anxiety disorders. For example, GAD is thought to be related to inhibitory avoidance and PD to the escape response. (Bailey et al. 2013; Dell'Osso et al. 2010; Graeff and Del-Ben 2008)

The noradrenergic neurons seem to be involved in response to fear, stress and arousal through sympathetic autonomic nervous system. Noradrenalin is released in the amygdala in response to aversive stimuli and is important in

acquisition and consolidation of emotional memory. On the other hand, it also seems to play a role in extinction learning. Thus, the α_2-adrenergic receptor antagonist yohimbine, which increases noradrenergic activity in the locus coeruleus, induces anxiety but also enhances extinction learning, reducing the sessions needed in exposure therapy. In turn, some experiments have suggested that β-adrenoceptor antagonist propranolol inhibits fear memory consolidation and response and could be prophylactic against PTSD, but would not work if administered after the trauma and could even be counterproductive with behavioural therapy. (Bailey et al. 2013; Dell'Osso et al. 2010; Mathew and Ho 2006)

It has been suggested that inhibitory GABAergic neurotransmission in the amygdala could have a central role in modulating anxiety-related behaviour. GABA receptor antagonists have been seen to be anxiogenic, whereas agonists decrease fear and anxiety. GABAergic receptors are also the target of benzodiazepines and related drugs. (Nuss 2015)

A few other neurotransmitters, such as opioid peptides and endocannabinoids, have been suggested to be involved in the pathophysiology of anxiety disorders. There is some evidence that opioid receptor signalling may enhance physical ability and motivation to escape in a threatening situation, but may result in depressive and anxious behaviour in response to chronic and inescapable stress. The endocannabinoid system is also highly reactive to acute stress. However, it has been suggested that chronic stress may cause a breakdown in endocannabinoid signalling and damage an endogenous buffer system to stress in the brain. (Bailey et al. 2013)

2.2.2.4 Structural and functional changes in the brain

Dysfunction in the limbic system, including amygdala and hippocampus, has been presented to play a crucial role in the pathogenesis of anxiety. The amygdala is a central structure not only involved in emotional processing and attention regulation in threat-response behaviour, but also in reward and motivational processing (Aouizerate et al. 2004; Tseng et al. 2014). Several studies have found hyper-responsivity of amygdala to negative stimuli among those with anxiety disorders. Further, larger amygdala volumes have been found in GAD patients compared to controls (Morris 2001; Newman et al. 2013; Spence and Rapee 2016; Tseng et al. 2014). It has also been noticed that this hyperactivation vanished as a result of successful treatment with cognitive behavioural therapy (Nuss 2015). The amygdala receives information on potential negative stimuli from the thalamus and the sensory association cortex. Neuronal projections from the amygdala lead to the hypothalamus and brainstem, resulting in somatic manifestations of anxiety, and to other basal forebrain nuclei, which may contribute to dysphoria in anxiety disorders. It has been suggested that the medial prefrontal cortex has a role in the regulation of experience of anxiety through the “top-down”

control, modulation of neuronal activity in the amygdala, which leads to inhibition of output from the amygdala. Interestingly, the medial prefrontal cortex has been found to be hypoactive in anxiety disorders such as PTSD and GAD in neuroimaging studies (Hovatta 2007; Nuss 2015). The neurobiology of fear is presented in Figure 1.

2.2.2.5 HPA axis

Output from amygdala to paraventricular nucleus of hypothalamus activates the corticotropin-releasing factor stress axis (Ninan and Dunlop 2005). HPA axis abnormalities, such as elevated stress hormone levels, have been detected in anxiety disorders (Bailey et al. 2013; Spence and Rapee 2016). Nevertheless, some differences have been noticed between different types of anxiety disorder: plasma cortisol levels increase in situations which induce anticipatory or generalized anxiety, but not during panic attacks. The explanation to this controversy may be the neural pathway passing from periaqueductal grey to hypothalamus and mediating the inhibition of the HPA axis. It has been suggested that panic is associated with defense reactions against proximal threat, integrated into the primitive structures of hindbrain which inhibit the HPA axis. On the other hand, anxiety is related to defense reactions against potential or distal threat integrated into limbic forebrain structures, prefrontal cortex, amygdala and hippocampus (Graeff and Del-Ben 2008).

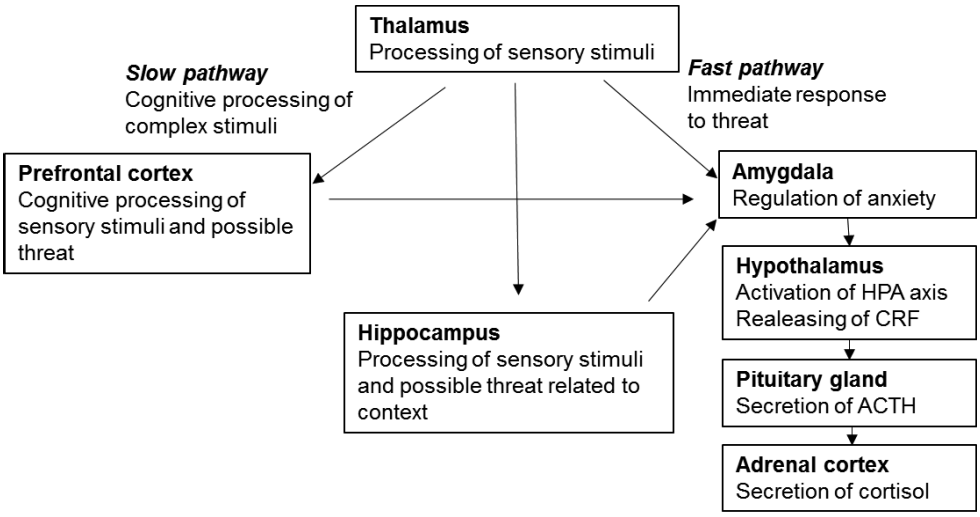


Figure 1. The neurobiolology of fear, based on Hovatta, 2007.

2.2.3 VULNERABILITY TO DEPRESSIVE AND ANXIETY DISORDERS IN ADOLESCENCE AND YOUNG ADULTHOOD

The incidence of depressive and anxiety disordes is highest in adolescence and young adulthood (Kessler et al. 2007). Previous findings suggest that this may be related to alterations in typical adolescent maturation processes together with psychosocial factors, biological and/or environmental factors (Paus et al. 2008). One of the neurobiological models explaining typical adolescent behaviour suggests that adolescence is characterized by an imbalance between relatively early maturation of subcortical areas and the more delayed maturation of prefrontal control areas. In emotional situations this may result in a more mature limbic and reward system to prevail over the prefrontal cortex exercising control functions. Hence, rewards and emotions affect the behaviour of adolescents probably more than rational decision-making processes. In terms of evolution, this typical cognitive style may be optimal considering developmental tasks in youth, such as establishment of intimate relationships, development of identity, future perspectives, independence, self-confidence, self-control and social skills. On the other hand, this high plasticity makes adolescents vulnerable to harmful influences (Konrad et al. 2013).

In adolescence, rising concentrations of sex hormones also affect neural networks by steroid receptors. Noteworthy is that increasing androgen levels inhibit the hypothalamic secretion of corticotropin-releasing hormone, whereas oestrogen upregulates the HPA axis. This may lead to hypersensitivity to stress in girls, while androgens make boys more resilient to it. This may partly explain why depression rates are twice as high in women as those in men; a difference that emerges during adolescence. (Naninck et al. 2011)

2.3 EPIDEMIOLOGY OF DEPRESSIVE AND ANXIETY DISORDERS

2.3.1 KEY CONCEPTS OF EPIDEMIOLOGY

In epidemiological studies, for analysing disease, two key concepts are used:

Incidence: the number of new cases of the disease within a specific period of time (Woodward 1999)

Prevalence: the number of existing cases of the disease at a particular point in time (Woodward 1999)

2.3.2 DEPRESSIVE DISORDERS

2.3.2.1 Global prevalence of depressive disorders

Since the 1970s, the introduction of specific diagnostic criteria for mental disorders, and development of fully structured research diagnostic interviews, has made possible cross-national synthesis of psychiatric epidemiological surveys. At the turn of the millennium, the World Health Organization (WHO) launched the World Mental Health (WMH) Survey, which used the Composite International Diagnostic Interview (CIDI) for diagnostics, and studied the epidemiology of mental disorders worldwide. According to the survey, from 18 countries in Africa, Asia, the Americas, Europe and the Middle East, the pooled 12-month prevalence of major depressive episode (MDE) was 5.5% in high-income and 5.9% in low- to middle-income countries, varying from 2.2% in Japan to 10.4% in Brazil. Thus, though the prevalence was very similar in high-income and other countries, regional variation existed in spite of a consistent study methodology. (Bromet et al. 2011)

A recent systematic review found the highest prevalence estimates in South Asia and Africa/Middle East and the lowest in East/Southeast Asia. The global point prevalence of MDD was assessed to be 4.7% (4.4-5.0%), and the pooled annual incidence 3.0% (2.4-3.8%) (Ferrari et al. 2013c). Other systematic reviews and meta-analyses have found the average 12-month prevalence ranging from 4.1% to 6.9% (Eaton et al. 2008; Waraich et al. 2004; Wittchen et al. 2011). Waraich et al. present a lifetime prevalence of 6.7% for MDD. Lifetime prevalence estimates for MDD/MDE have varied widely regionally, the majority being between 8-16% (Andrade et al. 2003; Kessler et al. 2003b; Waraich et al. 2004). Several studies have found higher prevalence for women compared to men; the female to male odds ratios in most studies ranging from 1.2 to 3.1 (Andrade et al. 2003; Angst et al. 2002; Ferrari et al. 2013c; Kuehner 2003).

Estimates on the prevalence of dysthymia are variable. The Global Burden of Disease 2010 study combined 1-, 3-, 6- and 12-month prevalence and gave a period prevalence estimate of 1.6% for dysthymia. The mean incidence of raw data was 1.2% (Charlson et al. 2013). In the World Mental Health Survey, the 12-month prevalence of dysthymia ranged from 0.1-1.5%, whereas lifetime estimates varied between 0.1-2.7%. Interestingly, higher estimates were found in high-income countries rather than those with a low or middle income (Gureje 2011). Another review established a pooled 1-year prevalence of 2.5% and lifetime prevalence of 3.6% for dysthymia (Waraich et al. 2004). Again, prevalence rates for women were higher than for men (Charlson et al. 2013; Waraich et al. 2004).

There has previously been controversy about whether the prevalence of depressive disorders has been increasing over the last decades (Baxter et al. 2014; Compton et al. 2006; Ferrari et al. 2013a; Markkula et al. 2015). The

most recent study from the United States found that the prevalence of depression had increased between 2005 and 2015, and the rate of increase was more rapid among adolescents and young adults (Weinberger et al. 2018).

2.3.2.2 Prevalence of depressive disorders in Finland

In Finland, the Health 2000 Survey and its follow-up Health 2011 Survey investigated mental health of the general population aged 30 years and over using the Munich Composite International Diagnostic Interview (M-CIDI) (Wittchen et al. 1998a). Markkula et al. found that the 12-month prevalence of MDD had increased, being 4.9% in 2000 and 7.4% in 2011. The female–male odds ratio for MDD was 2.33 (10.0% vs. 4.4%) in 2011. Corresponding figures for dysthymia were 2.5% in 2000 and 4.5% in 2011. The increase in the prevalence of depressive disorders was statistically significant among women (Markkula et al. 2015; Pirkola et al. 2005). Previously, the Mini Finland Health Survey, carried out in 1978-1980, found a prevalence of 4.6% for neurotic depression among adults 30 years or older using Present State Examination (PSE) (Lehtinen et al. 1990b). As a part of the national Finnish Health Care Survey (FINHCS `96), participants aged 15-75 years were interviewed with the Short Form of the University of Michigan CIDI (UM-CIDI) and the 12-month prevalence of major depressive episode was 9.3% (Lindeman et al. 2000). In all these studies, depression was more prevalent among women than men. In the Finnish subsample of the European Outcomes of Depression International Network (ODIN) study, the annual incidence of all depressive disorders was 2.8% and for first-time episodes 2.1% (Lehtinen et al. 2005).

2.3.2.3 Prevalence of depressive disorders among young adults

The prevalence of depressive disorders is relatively low until early adolescence, whereafter it starts to increase linearly through late middle age, increasing then more gradually. (Charlson et al. 2013; Hasin et al. 2005; Kessler et al. 2007; Kessler and Bromet 2013). In the World Mental Health Survey, the youngest median estimate for age of onset of MDE was 18.8 years in Shenzhen and the oldest was 31.9 years in Pondicherry, and there was no difference between high-income and middle-income countries. The risk period for onset of MDE peaked between mid to late adolescence and the early 40s (Kessler and Bromet 2013).

Though young adulthood is the time period where the prevalence of depressive disorders is at its peak, there are relatively few studies focusing on depression in this age group. In Finland, the Mental Health in Early Adulthood (MEAF) study investigated depressive disorders among young adults aged 19-34 years. Lifetime prevalence rates of 13.8% for MDD, 0.4%

for dysthymia and 3.7% for depressive disorder NOS, using the Structured Clinical Interview for DSM-IV (SCID-I), (First et al. 2001) were found (Suvisaari et al. 2009). Corresponding figures in the National Comorbidity Survey Replication (NCS-R) in the age group of 18-29 years were 15.4% for MDD and 1.7% for dysthymia (Kessler et al. 2005). Another survey from the United States found the lifetime prevalence of 12.0% for MDD in the same age group (Hasin et al. 2005). Haarasilta et al. found a 12-month prevalence of 9.4% for MDE among young adults in the FINHCS ´96 study (Haarasilta et al. 2001).

Globally, 12-month prevalence rates of 6.4% and 10.0% for MDD, 2.1% for dysthymia (Hasin et al. 2005; Jacobi et al. 2015) and 4.4-15.1% for any mood disorder have also been reported for young adults (Alonso et al. 2004b; Jacobi et al. 2004; Jacobi et al. 2015). The National Survey on Drug Use and Health (NSDUH) study in the US found the 12-month prevalence of MDE increased from 8.7% in 2005 to 11.3% in 2014 among adolescents, and from 8.8% to 9.6% among young adults. The trend was larger and statistically significant only among 12-20 years old participants (Mojtabai et al. 2016).

2.3.3 ANXIETY DISORDERS

2.3.3.1 Global prevalence of anxiety disorders

Anxiety disorders are the most prevalent group of mental disorders in many countries. Nevertheless, there is marked cross-national variation in prevalence estimates. In addition to methodological variations between studies, attitudes towards, as well as experiencing and expressing of mental illness, may differ across countries, which may explain the variation. However, some disorders, such as specific phobias and generalized anxiety disorder seem to be more common, and agoraphobia and panic disorder less common across regions. (Remes et al. 2016; Stein et al. 2017)

Recent reviews have found a 12-month prevalence of 10.6% to 14.0% and a lifetime prevalence of 16.6% for total anxiety disorders (Ferrari et al. 2013c; Somers et al. 2006; Wittchen et al. 2011). The World Mental Health Survey found a median lifetime prevalence of 4.8-31.1% for anxiety disorders across countries with 9.9-16.7% interquartile range (Kessler et al. 2007). Highest prevalence rates have been reported previously in Europe, North America and Australia (Baxter et al. 2013). In a recent review about trends in the global prevalence of anxiety disorders, Baxter et al. found the lowest point prevalence in East Asia, and the highest in North America and the North African/Middle East region. Global age-standardized point prevalence was 3.8% in 1990 and 4.0% in 2010. Thus, no evidence for increasing prevalence of anxiety disorders was found. The prevalence was higher in women (1.9 vs. 1), which is in line with other studies (Baxter et al. 2014; Somers et al. 2006).

A recent review presented that prevalence is also high among young adults and people with chronic diseases (Remes et al. 2016).

2.3.3.2 Prevalence of anxiety disorders in Finland

In Finland, the Health 2000 Survey investigated the prevalence of CIDI DSM-IV panic disorder, social phobia, agoraphobia and generalized anxiety disorder. The 12-month prevalence of anxiety disorders was 4.2%, panic disorder being the most prevalent (1.9%) (Pirkola et al. 2005). In the Mini Finland Health Survey, anxiety or phobic neurosis was the most common class of mental disorder with a prevalence of 6.2% (Lehtinen et al. 1990b). Both studies found anxiety disorders to be more prevalent among women than men.

2.3.3.3 Prevalence of anxiety disorders among young adults

Anxiety disorders as a class consist of various disorders with different age of onset distributions. Globally, phobias and separation anxiety disorder have the earliest ages of onset, the median varying between 7-14 years. Generalized anxiety disorder, panic disorder and post-traumatic stress disorder have their onset much later in life (median age 24-50 years), and the cross-national variation of age of onset is larger than in phobias or separation anxiety disorder. (Kessler et al. 2007)

In the Finnish MEAF study, the lifetime prevalence of anxiety disorders among young adults was 12.6%; the most common anxiety disorders were anxiety disorder NOS and social phobia and the least common generalized anxiety disorder (Suvisaari et al. 2009). The NCS-R study in the USA found a much higher lifetime prevalence of 30.2% for any anxiety disorder among participants aged 18-29 years. Social phobia and specific phobia were the most common anxiety disorders, whereas agoraphobia was the least common (Kessler et al. 2005). 12-month prevalence rates for any anxiety disorder among young adults have varied between 7.0-18.1%, although the included disorders differed slightly across studies (Alonso et al. 2004b; Jacobi et al. 2004; Jacobi et al. 2015).

2.4 COURSE AND OUTCOME OF DEPRESSIVE AND ANXIETY DISORDERS

2.4.1 COURSE AND OUTCOME OF DEPRESSIVE DISORDERS

The natural course of depression has been known from the late nineteenth century after Emil Kraepelin`s longitudinal study. He introduced, as did researchers after him, that depressive disorders are commonly recurring and

sometimes chronic disorders (Charlson et al. 2013; Fox 2002; Hardeveld et al. 2010). He observed that the interval between episodes decreased over time and episode duration within individuals tended to be constant lasting 6-8 months on average, but also episodes of 2-4 years were "not at all rare" (Fox 2002).

After Kraepelin, the course of depression has been examined using population-based samples, which have estimated the median duration of MDE to be 3–4 months (Eaton et al. 2008; Kessler et al. 2003b; Spijker et al. 2002) and recurrent episodes to be slightly shorter than initial episodes (Eaton et al. 2008; Spijker et al. 2002). Compared to MDD, which has an episodic nature, dysthymic disorder is more chronic and remission rates are lower (Charlson et al. 2013).

2.4.1.1 Remission, recurrence and persistence of depressive disorders

In the Finnish Health 2011 Study, the course of depressive disorders was investigated among participants aged 30 years and over in an eleven-year follow-up in a general population sample. It showed that 21% of participants with baseline MDD and 27% of those with baseline dysthymia received a diagnosis of any depressive disorder after 11 years of follow-up. A diagnosis of any depressive, anxiety or alcohol use disorder in the follow-up was received by 34% of those in MDD group and 43% of dysthymia group. (Markkula et al. 2016)

These figures are in line with another recent population study, the Netherlands Mental Health Survey and Incidence Study (NEMESIS), which found that 21% of persons with a pure depression at baseline and 35% of those with comorbid depressive and anxiety disorders had depressive disorders after 7 years of follow-up. About 61% of all participants with depressive and/or anxiety disorders at baseline were free of these diagnoses in the follow-up (Rhebergen et al. 2011). In Canada, the national Population Health Survey also showed a quite favourable course of depression, as 77% of those with a major depressive episode at baseline did not screen positive with Composite International Diagnostic Interview-Short form (CIDI-SF) (Kessler et al. 1998a) for depression after 2 years, and 94% had remitted by 12 years (Fuller-Thomson et al. 2014). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) in the United States also investigated the course of chronic depression defined as a current episode of MDD of >2 years' duration and/or dysthymic disorder. Results showed that 67% of cases did not meet the criteria for dysthymic disorder nor MDD any more in the 3 years of follow-up (Agosti 2014).

The Early Developmental Stages of Psychopathology (EDSP) study followed up a community sample of adolescents and young adults aged 14-24 years over 10 years (Beesdo-Baum et al. 2015). In this study, 30% of those with clinical depression were still affected at 20-month follow-up, while 28% had depressive symptoms and 42% had no depressive symptoms (Oldehinkel

et al. 1999). Another study focusing on adolescents aged 12-17 years was carried out in the schools of Bremen, Germany. Accordingly, 76% of those who received a diagnosis of MDD at baseline did not meet the same diagnosis after 15 months, and 49% did not meet the criteria for any DSM-IV disorder (Essau 2007).

Longitudinal studies initiated several decades ago offer an opportunity for longer follow-up periods, though the methodology of these studies often differs from recent ones. The Lundby study, with an exceptionally long follow-up period of 30-49 years, was started as early as 1947. This study found a recurrence rate of about 40% for depression, varying between 17% and 76% and increasing with follow-up time (Mattisson et al. 2007). In the Upper Bavarian Longitudinal Study, 24% of those with a pure depression at baseline and 32% of those with depression and anxiety had depression after 25 years of follow-up, whereas 73% of those with pure depression and 66% of comorbid cases had no anxiety or depressive disorders (Fichter et al. 2010). In the Zurich cohort Study initiated in 1978, after 7 years of follow-up 47% of those with pure depression at baseline and 45% of those with comorbid depression and panic had no diagnosis, whereas half of both groups had depression (Vollrath and Angst 1989). A more recent follow-up of the same cohort found that pure or comorbid depression is more stable than anxiety alone over time, and comorbid depression and anxiety tend to be more persistent than either syndrome alone (Merikangas et al. 2003). The Baltimore Epidemiologic Catchment Area (ECA) study with 23 years of follow-up showed that about half of participants with a first-onset MDD episode recovered and had no further episodes. In 35% of cases the disorder was recurrent and in 15 % unremitting (Eaton et al. 2008).

According to clinical studies, prognosis of depressive disorders seems to be poorer than in population–based studies. In their review, Hardeveld et al. found the recurrence of MDD to be 85% in 15 years in specialized mental healthcare settings against 35% found in the ECA Study. One included study from primary care found a recurrence rate of 31% after 1 year (Hardeveld et al. 2010). Clinical studies have found remission rates of 43-50% after 2-5 years of follow-up (Holma et al. 2008; Stegenga et al. 2012).

In a recent study on prognosis of depression, longer follow-up and broader diagnostic conceptualization showed that the majority of patients had a disabling and chronic affective disorder and full recovery was rare. Thus, handling MDD as a narrowly defined and episodic disorder may underestimate the consequences of depression and the type of appropriate care. (Verduijn et al. 2017)

2.4.1.2 Quality of life in depressive disorders

Depressive disorders have a significant impact on quality of life of affected persons. In the Finnish Health 2000 survey among participants aged over 30 years, dysthymia and chronic anxiety disorders were associated with the

largest loss of health-related quality of life (HRQoL) among psychiatric disorders. At population level, depressive disorders accounted for the largest portion of loss of quality-adjusted life years before anxiety disorders and alcohol dependence (Saarni et al. 2007). When 29 major chronic conditions were investigated, depressive disorders had the third largest negative impact on HRQoL at individual level in Finland (Saarni et al. 2006). These results are in line with the population-based study in Sweden, which found the lowest quality of life among persons with depression (Burstrom et al. 2001).

The Finnish Health 2011 study found that those participants with depressive disorders at baseline who did not receive any psychiatric diagnosis in the follow-up still had lower quality of life compared with the general population (Markkula et al. 2016). In another community-based study, a history of depression had a negative effect on HRQoL of women during midlife without a current disorder (Joffe et al. 2012). However, it has also been seen that depressive patients may attain adequate mental health and global well-being after recovery (Koivumaa-Honkanen et al. 2008).

2.4.2 PREDICTORS OF OUTCOME IN DEPRESSIVE DISORDERS

2.4.2.1 Sociodemographic factors

Findings on studies examining sociodemographic factors as predictors of course and outcome in depressive disorders are somewhat inconsistent. A few studies have found that women have a higher risk of poor outcome than men (Colman et al. 2007; Eaton et al. 2008; Mueller et al. 1999; Spijker et al. 2001b), whereas most studies have found no difference between genders (Agosti 2014; Fuller-Thomson et al. 2014; Markkula et al. 2016; Rhebergen et al. 2011; Spijker et al. 2004). In some studies, older age has been a predictor of non-recovery (Agosti 2014; Klein et al. 2008; Penninx et al. 2011), but younger age has also been associated with poor outcome in a few studies (Eaton et al. 2008; Holma et al. 2008). Being single, divorced or widowed has been related to unfavourable course of depression (Agosti 2014; Colman et al. 2007; Eaton et al. 2008; Markkula et al. 2016; Mueller et al. 1999), as well as not having children (Colman et al. 2007).

Other sociodemographic factors which have been associated with unfavourable course of depression are low education, unemployment and socioeconomic adversity (Dowrick et al. 2011; Klein et al. 2008; Spijker et al. 2001b; van Beljouw et al. 2010; Viinamäki et al. 2006). Viinamäki et al. found that a rural area of residence in Eastern Finland, with higher unemployment and lower income than urban areas, was associated with non-recovery from major depression (Viinamäki et al. 2006). The effect of regional socioeconomic deprivation on persistence of depressive symptoms has also been noticed elsewhere (Ostler et al. 2001).

2.4.2.2 Psychosocial factors

Of psychosocial factors, lack of social support and loneliness have been associated with worse outcome of depressive disorders (Dowrick et al. 2011; Leskelä et al. 2006; Spijker et al. 2004; van Beljouw et al. 2010; Viinamäki et al. 2006). Controversially, a large family network was also found to predict a longer episode of depression in one study (Eaton et al. 2008).

Several studies have shown the effect of negative life events on the course of depression. Especially childhood adversities, such as sexual or physical abuse, parental addictions and poor maternal relationship, have been presented to predict unfavourable course (Agosti 2014; Dowrick et al. 2011; Essau 2007; Fuller-Thomson et al. 2014; Gilman et al. 2013; Klein et al. 2008; Nanni et al. 2012; Rhebergen et al. 2011). Particularly multiple and severe life events during adulthood seem to predict a worse prognosis in depression (Leskelä et al. 2006; Spijker et al. 2004; Tanskanen et al. 2004). However, childhood adversities have not been associated with outcome of depression in all studies (Markkula et al. 2016).

A family history of depression has also been related to a lack of recovery or a shorter time to recurrence (Dowrick et al. 2011; Hardeveld et al. 2013a), whereas greater family loading for chronic depression predicted depression severity and functional impairment in 10 years of follow-up (Klein et al. 2008). This may reflect the influence of both family environment and genetic risk of depression.

2.4.2.3 Clinical features

According to previous studies, the prognosis of depression is closely related to disorder-specific factors: a history of depression as well as longer duration of previous episodes or longer episode before the onset of treatment, the number of earlier episodes and symptom severity have all been identified as risk factors of poor prognosis of depressive disorders (Bulloch et al. 2014; Dowrick et al. 2011; Eaton et al. 2008; Hardeveld et al. 2010; Holma et al. 2008; Markkula et al. 2016; Mueller et al. 1999; Penninx et al. 2011; Spijker et al. 2001b; Spijker et al. 2004; van Beljouw et al. 2010; Viinamäki et al. 2006). Such symptom traits as suicidal behaviour, anhedonia and early awakening have also been found to predict a persistence of illness (Spijker et al. 2001b; Ten Have et al. 2017). A few studies have associated high neuroticism to predict a poor prognosis in depressive disorders (Rhebergen et al. 2009; Rhebergen et al. 2011; Spijker et al. 2001b).

Comorbid disorders have a negative impact on the outcome of depression. Particularly comorbid anxiety disorders are common and have been frequently found to predict an unfavourable course of depression (Agosti 2014; Holma et al. 2008; Lamers et al. 2011; Penninx et al. 2011; van Beljouw et al. 2010). Of psychiatric comorbidity, personality disorders and substance use disorders have also been found to be risk factors for negative outcomes

(Agosti 2014; Essau 2007; Holma et al. 2008; Viinamäki et al. 2006). Additionally, the presence of other health conditions such as chronic physical illness, pain and low physical functioning have been seen to predict persistence of depressive disorders (Fuller-Thomson et al. 2014; Rhebergen et al. 2009; Rhebergen et al. 2011; Spijker et al. 2004), although there have also been negative findings (Markkula et al. 2016).

2.4.2.4 Treatment-related factors

In NEMESIS, the use of professional care and more intensive care were associated with poor 1-year outcomes among participants with depressive disorders (Spijker et al. 2001a; Spijker et al. 2001b). The study of ten Have et al. found that longer duration of MDD episode was associated with psychotropic medication use and mental healthcare use (Ten Have et al. 2017). In some other studies, no association between treatment and outcome of depression was found (Dowrick et al. 2011; Hardeveld et al. 2013a; Prins et al. 2011a). These findings may be related to a previously noticed biasing effect in epidemiological studies: persons with more severe symptoms seek and receive treatment more often and are treated more intensively than those with milder symptoms (Bland et al. 1997; Prins et al. 2011a; Prins et al. 2011b; Verhaak et al. 2009).

In contrast to epidemiological studies, randomized clinical trials have provided evidence that antidepressive medication is effective in preventing relapse or recurrence in major depressive disorder (Sim et al. 2015). Guideline-concordant care has also been associated with improved outcomes in primary care patients with depression (Hepner et al. 2007).

2.4.2.5 Cognitive functioning

There is growing evidence that cognitive dysfunction is common in depressive disorders, even among young adults, at least in clinical study samples (Ahern and Semkovska 2017; Castaneda et al. 2008b; Papakostas 2014). It has been noticed that some deficits, such as problems in memory and decision making, are present early in the course of MDD and may even precede onset of the first episode (Trivedi and Greer 2014). A recent systematic review and meta-analysis already found significant cognitive impairment across most cognitive domains during first-episode depression, while some dysfunction persisted upon remission (Ahern and Semkovska 2017; Gonda et al. 2015). However, Castaneda et al. found only minimal cognitive deficits on cognitive functioning among young adults with lifetime depressive disorders in the general population (Castaneda et al. 2008a). Treatment seeking was associated with cognitive deficits, suggesting that cognitive impairment may be more prevalent in clinical samples (Castaneda et al. 2010).

Most studies about the effect of cognitive deficits on the course of depressive disorders have been based on clinical samples. It has been suggested that cognitive dysfunction decreases coping capacities and influences therapeutic compliance and cooperation. Hence, they influence significantly such clinical outcomes as therapeutic response, episode duration and risk of relapse (Gonda et al. 2015; Papakostas 2014). Additionally, they seem to mediate functional decline and psychosocial impairment, such as performance at work, and also affect quality of life (Gonda et al. 2015; McIntyre et al. 2013).

In the study of Airaksinen et al., depressed participants from a population-based sample were followed up for three years. They found that despite symptomatic and social functional recovery, episodic memory dysfunction persisted over the follow-up period. Additionally, those who fulfilled the criteria for DSM-IV depression at the three-year follow-up, did not differ from those in remission in episodic memory performance at baseline (Airaksinen et al. 2006).

2.4.3 COURSE AND OUTCOME OF ANXIETY DISORDERS

Anxiety disorders are a variety of disorders which in general have a relatively chronic course with low rates of recovery and high probability of recurrence (Bruce et al. 2005). However, the course and outcome differ between individual disorders. Social phobia is often seen as the most chronic, and panic disorder without agoraphobia characterized by frequent remission and relapse rates (Bruce et al. 2005; Hendriks et al. 2013; Yonkers et al. 2003).

2.4.3.1 Remission, recurrence and persistence of anxiety disorders

NEMESIS, a population-based study from the Netherlands, followed up adult participants with a CIDI diagnosis of depressive and/or anxiety disorders. Of those with anxiety disorders at baseline, 37% also had pure or comorbid anxiety disorders after 7 years, and 10% had pure depressive disorders. The corresponding figures were 35% and 17% for those with comorbid anxiety and depressive disorders (Rhebergen et al. 2011). NESARC study investigated longitudinal course of panic disorders and found that 75% of participants with panic disorder and 67% of those with panic disorder with agoraphobia (PDA) remitted in the 3 years of follow-up. On the other hand, relapse for those with lifetime but not current disorder at baseline was also relatively common, 12% for PD and 21% for PDA (Nay et al. 2013).

The EDSP study of adolescents and young adults in a community sample in Germany investigated the longitudinal course of different anxiety disorders over 10 years. The study showed that 16% of those with a social anxiety disorder met the diagnostic criteria again, whereas 15% completely remitted with no social anxiety symptoms or other mental disorders during

follow-up (Beesdo-Baum et al. 2012). Regarding PTSD, the remission rate was 43% during the follow-up period, while 26% still fulfilled diagnostic criteria for PTSD in the follow-up (Perkonigg et al. 2005). Of those with specific phobia at baseline, 41% received the same diagnosis at 10-year follow-up. A persistence (the proportion of years affected since onset of a disorder) of 70% for any anxiety disorder was found (Beesdo-Baum et al. 2015). In another German study among adolescents from Bremen, 23% of those with DSM-IV anxiety disorders at baseline still had an anxiety disorder at follow-up; 42% of them had no disorders in the follow-up (Essau et al. 2002).

The Lundby Study found that 54% of men and 71% of women with anxiety disorders had no mental illness after a 25-year follow-up period. For about 25% of men and 15% of women, the course of disorder was chronic, as the first episodes lasted for 5-15 years (Gräsbeck et al. 1998). In the Upper Bavarian Longitudinal Community Study, 21% of those with pure anxiety and 15% of those with comorbid depressive and anxiety disorders at baseline had anxiety disorders after 25 years, while 62% of those with pure anxiety and 66% of those with comorbidity had no anxiety or depressive disorders. The transition from anxiety syndrome to depressive syndrome was more likely than the reverse (Fichter et al. 2010). The Zurich Cohort study found that 18% of participants with panic disorder at baseline, had panic disorder after 7 years follow-up, and 59% had no diagnosis (Vollrath and Angst 1989). In the later follow-up of the Zurich Cohort, pure anxiety states seemed to transform to pure depression or comorbid anxiety and depression through adulthood (Merikangas et al. 2003).

Clinical studies show a rather chronic course for anxiety disorders. The Harvard/Brown Anxiety Disorders Research Program (HARP) was a prospective, naturalistic, longitudinal, multicentre study of adults with a current or past history of anxiety disorders. It investigated the course of panic disorder, social phobia and generalized anxiety disorder. Social phobia appeared to be the most chronic, with 63% of the patients still being in the original intake episode after 12 years. Participants with panic disorder were most likely to achieve recovery from the intake episode by year 12 with 82% probability. The same figure for generalized anxiety disorder was 58%, for panic disorder with agoraphobia 48% and for social phobia 37%. Of recovered subjects, those with social phobia and generalized anxiety disorder were less likely to have a recurrence over 12 years, with probabilities of 39% and 45%, as those with panic disorder with and without agoraphobia had almost similar probabilities of recurrence (58% and 56%). The average amount of time patients remained ill during the follow-up period was 80% for social phobia, 78% for panic disorder with agoraphobia, 74% for generalized anxiety disorder and 41% for panic disorder without agoraphobia (Bruce et al. 2005). In a recent meta-analysis on the long-term outcome of OCD treated with serotonin reuptake inhibitors and/or cognitive behavioural

therapy, the pooled remission rate was 53%, when a mean follow-up time was 4.9 years (Sharma et al. 2014).

The Netherlands Study of Depression and Anxiety (NESDA) investigated symptom course trajectories of anxiety disorders over a 6-year time period and found that in 44% of the participants symptoms of anxiety and avoidance improved, in 24% remained stable, in 25% slightly increased and in 7% severity increased (Spinhoven et al. 2016).

2.4.3.2 Quality of life in anxiety disorders

Anxiety disorders have a significant impact on quality of life (QOL). In the Health 2000 study, generalized anxiety disorder and social phobia in addition to dysthymia were associated with the largest loss of health-related quality of life among mental disorders at individual level (Saarni et al. 2007). Furthermore, anxiety disorders had the second largest negative impact on HRQoL, just before depressive disorders, when 29 chronic disorders were considered (Saarni et al. 2006).

A meta-analytic review of Olatunji et al. presented that overall quality of life is poor among anxiety patients compared to non-clinical controls across all anxiety disorders. When specific domains of QOL were considered, impairment seemed to be particularly prominent among those with post-traumatic stress disorder (Olatunji et al. 2007).

Though there is some evidence of improvement of QOL after successful pharmacological or cognitive behavioural treatment, there are also findings that QOL of anxiety disorder patients remains lower compared to the general population after treatment (Olatunji et al. 2007). The study of Joffe et al. on quality of life of midlife women found that a previous history of depression and anxiety disorders had a negative effect on health-related quality of life in the absence of a current illness, but the impact of anxiety disorders alone was more limited, affecting mainly the “role-physical” dimension of HRQOL (Joffe et al. 2012).

2.4.4 PREDICTORS OF OUTCOME IN ANXIETY DISORDERS

2.4.4.1 Sociodemographic factors

It has been suggested that female gender may be associated with especially transient and episodic forms of internalizing psychopathology because of more reactivity to stress during adulthood and adolescence (Olino et al. 2010). This has been seen especially in studies on panic disorders, which have shown that remission, and also recurrence, to be more common for women than men. It has been suggested that greater carbon dioxide sensitivity and fluctuation in progesterone levels altering respiratory rates

could influence the higher susceptibility to panic attacks in women (Batelaan et al. 2010a; Batelaan et al. 2010b; Francis et al. 2007; Nay et al. 2013; Yonkers et al. 1998; Yonkers et al. 2003). On the other hand, some studies have found male gender to predict a longer duration of panic disorder and non-remission of OCD (Batelaan et al. 2010b; Sharma et al. 2014). Some studies have shown anxiety disorders to be more persistent in women (Grills-Taquechel et al. 2010; McLean et al. 2011), while most studies have found no gender differences in the course of these disorders (Beard et al. 2010; Essau et al. 2002; Essau et al. 2018; Marcks et al. 2011; Perkonigg et al. 2005; Rhebergen et al. 2011; Scholten et al. 2013; van Beljouw et al. 2010).

With respect to the effect of age on the course of anxiety disorders, findings have been mixed as well. There is some evidence of a worse prognosis for younger persons with anxiety disorders (Nay et al. 2013; Ramsawh et al. 2009), but a few studies have also found an association of older age with poor outcome (Essau et al. 2002; Penninx et al. 2011), while several studies have found no effect of age on the course of anxiety disorders (Batelaan et al. 2010a; Beard et al. 2010; Francis et al. 2007; Nelson and Rice 1997; Perkonigg et al. 2005; Scholten et al. 2013). An earlier age of onset has been associated with a poorer course of anxiety disorders in a number of studies (Francis et al. 2007; Nelson and Rice 1997; Ramsawh et al. 2011), though others have not found this association (Marcks et al. 2011; Scholten et al. 2013). A recent meta-analysis by Sharma et al. found that persons with onset in late adolescence or young adulthood may have a better outcome of OCD than those affected earlier (Sharma et al. 2014). Unemployment, lower education, economic difficulties, not being married and having no children have also been associated with different aspects of poor prognosis in anxiety disorders (Batelaan et al. 2010a; Colman et al. 2007; Marcks et al. 2011; Nay et al. 2013; Scholten et al. 2013; van Beljouw et al. 2010; Vriends et al. 2007).

2.4.4.2 Psychosocial factors

Psychosocial factors, including poor family relationships, smaller personal networks as well as lack of social acceptance and support have been related to chronic or severe course of anxiety disorders (Prins et al. 2011a; Steinert et al. 2015; Weisberg 2009). Childhood psychosocial environment and life adversities also seem to especially affect the course of anxiety disorders (Rhebergen et al. 2011). Childhood trauma and maladaptive family functioning, such as abuse, neglect, family violence and parental mental illness, substance use disorders and criminality have been found to be associated with persistence and recurrence of anxiety disorders (Hovens et al. 2012; Olino et al. 2010; Scholten et al. 2013). The EDSP study found that lack of emotional warmth and dysfunctional characteristics, especially in interaction with parental psychopathology, predicted higher persistence of social phobia (Knappe et al. 2009). Parental history of anxiety or depressive disorders have also been found to predict a persistence of anxiety disorders,

which may be related to the influence of family environment or genetic risk of these disorders (Beesdo-Baum et al. 2012; Olino et al. 2010).

Nevertheless, there is also evidence of the effect of later life adversities on the course of anxiety: ongoing difficulties and negative life events, financial difficulties, higher number of, and stress related to, daily hassles as well as limited positive life events have predicted poorer prognosis of anxiety disorders (Batelaan et al. 2010a; Batelaan et al. 2010b; Essau et al. 2002; Nay et al. 2013; Vriends et al. 2007).

2.4.4.3 Clinical features

Different clinical features are noteworthy predictors of the course of anxiety disorders. Several studies have found comorbid mental health problems, especially depressive and other anxiety disorders, to predict an unfavourable course in anxiety disorders (Beard et al. 2010; Bruce et al. 2005; Francis et al. 2007; Hendriks et al. 2013; Keller 2003; Marcks et al. 2011; Merikangas et al. 2003; Nay et al. 2013; Nelson and Rice 1997; Penninx et al. 2011; Perkonigg et al. 2005; Steinert et al. 2015). Comorbid personality disorders, substance use disorders and somatoform disorders have also been presented to predispose to worse outcomes in anxiety (Bruce et al. 2005; Essau et al. 2002; Keller 2003; Nelson and Rice 1997; Perkonigg et al. 2005; Verges et al. 2014; Weisberg 2009), whereas fewer lifetime psychiatric disorders and better mental health have been related to recovery (Vriends et al. 2007). Comorbid physical health problems and low physical functioning have also been associated with poor prognosis (Rhebergen et al. 2011; Steinert et al. 2015).

Some personality traits, including high neuroticism, anxiety sensitivity, behavioural inhibition and harm avoidance, predict a more unfavourable course in anxiety disorders (Beesdo-Baum et al. 2012; Naragon-Gainey et al. 2013; Rhebergen et al. 2011; Scholten et al. 2013; Vriends et al. 2007). However, high self-esteem and self-worth, positive mental health and life satisfaction have been related to better outcomes (Batelaan et al. 2010a; Batelaan et al. 2010b; Grills-Taquechel et al. 2010; Trumpf et al. 2009; Vriends et al. 2007).

Disorder-related factors, such as longer episode of illness and more severe symptoms, have been presented to predict an unfavourable course in anxiety disorders (Batelaan et al. 2010a; Batelaan et al. 2010b; Beard et al. 2010; Beesdo-Baum et al. 2012; Hendriks et al. 2013; Nelson and Rice 1997; Sharma et al. 2014; van Beljouw et al. 2010). More catastrophic anxiety cognitions in social situations predicted higher persistence of social anxiety disorder, and severe avoidance, disability and impairment as well as lower psychosocial functioning have also been related to worse outcomes in anxiety disorders (Beesdo-Baum et al. 2012; Hendriks et al. 2013; Perez Benitez et al. 2013; Perkonigg et al. 2005; Scholten et al. 2013). In the Netherlands study of Depression and Anxiety, severity, duration and disability were better

outcome predictors than psychological characteristics neuroticism, extraversion, anxiety sensitivity, worry and rumination (Spinhoven et al. 2016).

2.4.4.4 Treatment-related factors

The same bias noticed in other mental disorders concerning treatment, has also been found in studies on anxiety disorders: those with a more complicated illness, in terms of more comorbidities, more severe symptoms or longer symptom duration, are more likely to perceive a need for care and seek treatment (Gräsbeck et al. 1998; van Beljouw et al. 2010). As the severity of a disorder is a significant predictor of outcome, paradoxically this may be seen as a worse outcome of treated participants. In fact, in the study of Perkonigg et al. more help seeking predicted a chronic course of PTSD (Perkonigg et al. 2005), while some studies have found no relationship between treatment and the course of anxiety disorders (Bruce et al. 2005; Prins et al. 2011a; Rodriguez et al. 2006). On the other hand, a recent review of Batelaan et al. found that relapse rates were higher among those participants with anxiety disorders who discontinued their antidepressant therapy compared to those who continued treatment up to 1-year follow-up, suggesting that treatment has a beneficial effect on the course of anxiety disorders (Batelaan et al. 2017).

2.4.4.5 Cognitive functioning

There are relatively few studies on cognitive functioning in anxiety disorders, especially among young adults, and most of them concern obsessive-compulsive disorder. However, impairment in verbal episodic memory and executive functioning has been seen in anxiety disorders in general in a population-based study (Airaksinen et al. 2005). The studies on OCD have found impairment in executive functioning and visual memory in young adulthood, and referred to a persistence of some cognitive deficits even after improvement of clinical symptoms (Castaneda et al. 2008b).

In the Mental Health in Early Adulthood (MEAF) study, participants with lifetime anxiety disorders in a population-based sample did not have major cognitive deficits compared to healthy controls, though those with a current disorder had a lower score in visual memory working tests. However, indicators of symptom severity, such as low current psychosocial functioning and use of psychotropic medication, were associated with problems in executive functioning, psychomotor processing speed and visual short-term memory (Castaneda et al. 2011).

A few clinical studies have investigated cognitive abilities as predictors of treatment response to cognitive behavioural or pharmacological therapy in obsessive-compulsive disorder, but findings have been mixed (Braga et al.

2016; Cavedini et al. 2002; D'Alcante et al. 2012). Furthermore, population-based studies on cognitive functioning as predictors of outcome in anxiety disorders among young adults are missing.

2.5 TREATMENT OF DEPRESSIVE AND ANXIETY DISORDERS

2.5.1 TREATMENT OF DEPRESSIVE AND ANXIETY DISORDERS ACCORDING TO GUIDELINES

In order to maintain a uniform and high level of care, treatment of mental disorders is instructed by evidence-based guidelines given by national institutions, such as American Psychiatric Association, National Institution for Health and Care Excellence, The Royal Australian and New Zealand College of Psychiatrists or Duodecim in Finland. (APA 2018; Duodecim 2018; NICE 2018; RANZCP 2018)

2.5.1.1 Treatment of depressive disorders

Treatment of acute depressive episode according to the Finnish guidelines and the efficacy of different types of treatment are summarized in Table 1 (Duodecim 2018; Taiminen 2013).

Table 1. Treatment of acute depressive episode, adapted from the Finnish guidelines

	Mild	Moderate	Severe	Psychotic	Cohen's d[a]
Psychotherapy	+	+	(+)		0.3-0.6
Antidepressive medication	+	+	+	+	0.3-0.4[b]
Antipsychotic medication (with antidepressive medication)	-	-	-	+	<0.3
Electroconvulsive therapy (ECT)	-	-	+	+	0.9
Antidepressive medication combined with CBT					0.7

[a] Cohen's d indicates the effect size and is defined as the difference between means in treatment and placebo groups divided by a standard deviation for the data
[b] The efficacy of one antidepressant

Selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and newer agents are recommended in guidelines as first-line medication, whereas tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors remain as second- or third-line antidepressive medication, because of tolerability and

safety issues as well as dietary and drug restrictions (Kennedy et al. 2016; RANZCP 2018). Combinations of different antidepressants have also been used, but the evidence of their efficacy is controversial and side effects are higher than in monotherapy (Kennedy et al. 2016). For treatment-resistant depression, lithium and thyroid hormones as adjuvant medication can also be used (Kennedy et al. 2016; Taiminen 2013). Antidepressant treatment is recommended to be maintained for 6-9 months after remission of symptoms and two years or more for those with a risk of recurrence (Kennedy et al. 2016).

For acute depression, several forms of psychotherapy, such as cognitive behavioural, interpersonal, psychodynamic and problem-solving therapy, have been demonstrated to be effective (Duodecim 2018; RANZCP 2018). Previous meta-analyses have shown that a combination of psychotherapy and medication is more effective than either type of treatment alone (Cuijpers et al. 2009a; Cuijpers et al. 2009b).

Other possible treatments in acute depressive episodes include bright light therapy for seasonal affective disorder (Duodecim 2018), and nowadays, neuromodulation treatment such as transcranial magnetic stimulation for patients with treatment-resistant depression or for patients who have not tolerated antidepressant treatment (Downar et al. 2016).

2.5.1.2 Treatment of anxiety disorders

The Finnish guidelines for treatment of anxiety disorders are currently under development. According to international guidelines, treatment options for anxiety disorders include psychological and pharmacological treatments, which have shown few differences in efficacy in the treatment of most anxiety disorders according to meta-analyses (Craske et al. 2017; Katzman et al. 2014). Results of a combination of psychotherapy and pharmacotherapy have been conflicting concerning different anxiety disorders. Thus, there is not unequivocal evidence on behalf of psychotherapy or pharmacotherapy as an initial treatment choice in most anxiety disorders, and hence patient preference may play an important role in this decision (Craske et al. 2017; Katzman et al. 2014). Only in specific phobia are exposure-based techniques the foundation of treatment, and pharmacotherapy has only a minimal role (Katzman et al. 2014).

Of psychological treatments, especially exposure based and other cognitive behavioural therapy protocols have demonstrated their efficacy in previous studies in treatment of anxiety disorders (Craske et al. 2017; Katzman et al. 2014; Stein and Craske 2017).

For most anxiety disorders, SSRIs and SNRIs have been recommended as first-line medication because of their better safety and tolerability than tricyclic antidepressants and MAOinhibitors, which have also shown some efficacy in treatment of anxiety disorders. Evidence of efficacy in some anxiety disorders has also been shown by atypical antipsychotics, non-

benzodiazepine anxiolytic buspirone and several anticonvulsants, especially pregabalin, which was not in use in Finland during this study. These agents are used as second-line, third-line, or adjunctive therapies. Pharmacotherapy has been recommended to be maintained from 6 to 24 months. (Katzman et al. 2014; Leinonen et al. 2018)

Benzodiazepines may also be used as adjunctive therapy early in treatment because of their rapid onset of action and assumed efficacy in the short term (Cloos and Ferreira 2009; Katzman et al. 2014). However, evidence of their effects even in the short term is solid only for panic disorder and GAD, whereas it is intermediate for social anxiety disorder and poor for PTSD and OCD (Dell'osso and Lader 2013). Furthermore, benzodiazepine use is associated with worse outcome in the long term because of the risk of dependence and side effects including daytime drowsiness, impairment of learning, psychomotor slowing and increased risk of accidents (Dell'osso and Lader 2013). Hence, they are not recommended as a first-line treatment in any anxiety disorder (Dell'osso and Lader 2013).

2.5.1.3 Criteria for minimally adequate treatment of depressive and anxiety disorders

International guidelines offer step by step recommendations on treatment for different types and stages of illness, and therefore cannot be used directly in population-based studies concerning treatment. Hence, simplified criteria for adequate treatment have been developed based on these guidelines.

Most population-based studies on treatment of depressive and anxiety disorders have used the same criteria for minimally adequate treatment: pharmacotherapy for at least 2 months with at least 4 visits with a physician, or at least 8 visits with any professional from mental health sector for psychotherapy lasting at least 30 minutes have been required. For depressive disorders, appropriate pharmacotherapy has included antidepressants, and in some cases mood stabilizers, whereas antidepressants and anxiolytics have usually been considered as proper medication for anxiety disorders. Based on guidelines, at least four visits have been seen to be necessary: the first visit is for diagnosing and initiating treatment, and the next three for monitoring effectiveness and side effects as well as changing medication during the acute and continuation phases of treatment. The number of psychotherapy visits has been decided based on the fact that clinical trials demonstrating the effectiveness of psychotherapy have generally included at least 8 visits. (Fernández et al. 2006; Kessler et al. 2003b; Wang et al. 2005b)

2.5.2 TREATMENT SEEKING AND TREATMENT ADEQUACY OF DEPRESSIVE AND ANXIETY DISORDERS ACCORDING TO POPULATION-BASED STUDIES

Mental and substance use disorders are among the leading causes of years lived with disability worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). Among them, mood disorders account for the largest proportion of disability-adjusted life years, followed by anxiety disorders (Whiteford et al. 2013). Depressive disorders were also a leading cause of burden of all diseases in 2010 (Ferrari et al. 2013b) and also the most costly disorders of the brain in Europe in 2010, whereas anxiety disorders took fourth place by causing marked direct healthcare costs (Gustavsson et al. 2011).

Still, these disorders are often undetected and undertreated, (Lecrubier 2007; Vermani et al. 2011) and median duration of delays making treatment contact for mental disorders are long (Wang et al. 2007b). In the World Mental Health Survey, the most common reason for not initiating treatment was low perceived need. Among those with a perceived need for treatment, attitudinal barriers, such as a desire to handle the problem alone, were more important than structural barriers, possibly caused by perceived stigma and labelling related to mental disorders. Structural barriers such as finance and lack of availability were common in people with severe symptoms who recognized a need for treatment, even in some developed countries (Andrade et al. 2014).

Adolescence and young adulthood are challenging life stages of transition to adulthood with identity formation and socialization. During this period, the incidence and prevalence of mental disorders is at its peak (Kessler and Walters 1998; Kessler et al. 2005; Newman et al. 1996), and untreated mental disorders may be especially detrimental as they have a significant impact on work and academic success, substance use and social interaction (Kessler et al. 1995; Kessler et al. 1998b; Weitzman 2004; Wittchen et al. 1998b).

2.5.2.1 Treatment seeking and treatment adequacy in depressive disorders

International population-based studies

Kohn et al. reviewed the treatment gap of mental healthcare, representing the absolute difference between the true prevalence of a disorder and the treated proportion of individuals affected by the disorder. They found a median treatment gap of about 56% for depression and dysthymia (Kohn et al. 2004).

The National Comorbidity Survey Replication (NCS-R), carried out in 2001–2002 in the United States, showed that 52% of 12-month cases with a CIDI diagnosis of MDD and 62% of those with dysthymia received healthcare treatment for their disorder. Among treated patients minimally adequate

treatment was received by 38% of those with MDD and 43% of those with dysthymia (Wang et al. 2005b). An earlier study focusing on MDD in the NCS-R found that clinical correlates of 12-month treatment and treatment adequacy were symptom severity, role impairment, duration, proportional days out of role during depressive episode and psychiatric comorbidity, whereas sociodemographic factors were not significantly related to treatment (Kessler et al. 2003b). The NCS-R also showed that 88-94% of people with lifetime depressive disorders eventually make treatment contact. Delays ranged from 7-8 years. Failure and delay in treatment seeking for mental disorders were related to early age of onset, older cohorts, male gender, being married, poorly educated and belonging to racial/ethnic minority (Wang et al. 2005a).

Another epidemiological survey from the same time period in the United States found very similar rates of treatment: 51% of those with 12-month major depression based on CIDI received pharmacotherapy or psychotherapy for their depression, and for 21% at least one type of therapy was guideline concordant. The criteria for guideline-concordant care were slightly less strict for psychotherapy requiring only 4 visits with a mental health professional in the past year. Factors related to not receiving any guideline-concordant care were male gender, lack of health insurance and belonging to ethnic groups of Mexican American, African American or Caribbean black. (González et al. 2010)

According to these and previous studies, there has been an increased trend in treatment of depression in the United States: during the NCS-R, 4% of the population had received treatment for depression in the past year, whereas the figure was 3% during the National Comorbidity survey in 1990-1991 and 2% during the Baltimore Epidemiologic Catchment Area (ECA) study in the early 1980s. The trend seems to be continuous, since in the most recent study in the US, almost 70% of those with lifetime DSM 5 MDD had had some lifetime treatment (Hasin et al. 2018). However, results concerning treatment adequacy have not improved as much (Kessler et al. 1999; Kessler et al. 2003b; Regier et al. 1990).

In Canada, a similar trend was noticed between 1994 and 2008 using data from a series of population-based surveys: the frequency of mental health treatment, especially the use of antidepressants, was increasing, though the prevalence of MDD had not changed over time (Simpson et al. 2012). The Canadian Community Health survey, conducted in 2002, found that 53% of participants with a 12-month CIDI diagnosis of MDD had visited a mental health professional at least once. Using similar criteria as the NCS-R, 29% of them had received guideline-concordant treatment. Predictors of receiving adequate treatment were having three or more chronic medical conditions, experiencing severe functional impairment, being at risk for suicide and having been treated in the mental health sector (Duhoux et al. 2009).

In the European Study of the Epidemiology Mental Disorders (ESEMeD), 5% had received a diagnosis of mood disorder during past year, and 37% of

these participants had sought help from the healthcare system during 12 months preceding the survey (Alonso et al. 2007). The proportion of treatment adequacy for major depressive episode was 46% among treated patients (Fernández et al. 2007). In Spain, of those with a 12-month major depressive episode, 41% had not used any type of service in the past year and only 15% had received adequate care. Psychotropic medication was the most used treatment. Those who had a comorbid mental disorder, who were unemployed or too disabled to work, who were middle-aged and who had moderate depression symptoms were more likely to use any health sector service (Gabilondo et al. 2011).

In the TürkSch Study, in the Izmir area, Turkey, conducted in 2007-2008, 57% of those with a CIDI diagnosis of MDD had not sought help, whereas 31% had sought help from mental health services. Of clinically depressed patients, 58% had received no treatment and 25% had received minimally sufficient treatment, for which the criteria were less strict than in most studies, requiring only 1 visit to health services, pharmacotherapy for at least 30 days and at least 4 sessions of psychotherapy. (Topuzoglu et al. 2015)

Finnish population-based studies

In Finland, healthcare use and treatment adequacy of depression has been investigated previously as part of the Health 2000 study. Among participants 30 years or older, 34% of those with a CIDI diagnosis of MDD and 59% of those with comorbid depressive and anxiety disorders had used health services. Service use of subjects with MDD was related to greater severity and perceived disability, psychiatric comorbidity and living alone (Hämäläinen et al. 2008). In the same sample, 31% of those with a CIDI diagnosis of MDD received antidepressants or psychological treatment or both, and 18% of them had received adequate treatment. In this study, female gender, being single, severe MDD, perceived disability and comorbid dysthymic disorder were factors related to the use of antidepressants, and perceived disability, comorbid anxiety disorder and being divorced were related to psychological treatment (Hämäläinen et al. 2009).

In the Finnish Health Care Survey conducted in 1996, the figures were quite similar to those in the Health 2000 study: 31% of men and 25% of women used health services for depression among those with a 12-month DSM-III-R major depressive episode. Longer duration, more severity and perceived disability were associated with use of health services. (Hämäläinen et al. 2004)

An earlier study, the Mini Finland Health Survey conducted in 1978–1980, presented that overall, 33.3% of those with depressive neurosis had used psychiatric treatment either in general or specialized health services. (Lehtinen et al. 1990a)

Studies among adolescents and young adults

According to NCS and NCS-R in the United States, attitudes to mental health treatment seeking improved and perceived stigma associated with mental problems declined between 1990 and 2003, more so among young than middle-aged people (Mojtabai 2007). However, in the National Epidemiologic Survey on Alcohol and Related Conditions in 2001-2002, fewer than a quarter of individuals aged 19-25 years with a mental disorder had sought treatment in the past year. Treatment rates were highest for mood disorders, as approximately 34% of them had used mental health services. The 12-month prevalence was approximately 7% for MDD and about 1% for dysthymia in this age range (Blanco et al. 2008). The NSDUH found a prevalence increase of MDE from 2005 to 2014 among adolescents and young adults in the US, but did not detect an overall change in healthcare contacts over time, suggesting that a growing number of young people do not receive treatment for their depression (Mojtabai et al. 2016).

The Healthy Minds Study, a web-based survey concentrating on college students, found that 22% of depressed students had received minimally adequate treatment. Women, students with higher depression scores, comorbid anxiety or suicidal ideation were more likely to have any treatment, whereas Asian students and students with less educated parents were less likely to receive any treatment. Among students who received at least some treatment, those with higher depression scores or a positive anxiety screen were more likely to receive minimally adequate treatment. (Eisenberg and Chung 2012)

Another web-based survey concerning university students in the US used the Patient Health Questionnaire (PHQ-9) for screening symptoms of depression. Overall, 45% of all participants with a positive screen for major depression, and 36% of those with pure depression had received psychotropic medication or psychotherapy during the previous year. Lack of perceived need, being unaware of services or insurance coverage, scepticism about treatment effectiveness, low socioeconomic background and being Asian or Pacific Islander were related to not receiving services among those who screened positive for depression or anxiety. (Eisenberg et al. 2007)

In Finland, as a part of a 5-year follow-up of high-school students, Aalto-Setälä et al. investigated 20-24 year old young urban adults in 1995 using semi-structured clinical SCAN (the Schedules for Clinical Assessment in Neuropsychiatry) interview. They found that 15% of these young adults suffered from depressive disorders. Approximately half of them had had a treatment contact with mental health services, and 34% had had a contact during index episode. Comorbidity was associated with treatment seeking, and women were more likely to report previous treatment contacts and intention to contact mental health services, but there was no gender difference in treatment contacts during the index episode. (Aalto-Setälä et al. 2002)

Another Finnish study investigated a sample of adolescents and young adults (15-24 years) from the Finnish Health Care Survey `96. About half of participants with a DSM-III-R major depressive episode were estimated to be in probable need of treatment, whereas 20.6% had actually sought help for their depression during the past year. Of the treatment users, only 14% (2 persons) had used antidepressant medication. (Haarasilta et al. 2003)

2.5.2.2 Treatment seeking and treatment adequacy in anxiety disorders

International population-based studies

In a recent study, Alonso et al. investigated the treatment gap of anxiety disorders from 23 community surveys in 21 countries of the World Mental Health Surveys. Investigating treatment in a variety of societies and healthcare systems, this worldwide research found requirement of only 1 month of medication and also accepted complementary alternative medicine and non-medical care for criteria of possibly adequate treatment. Of the participants, 10% had at least 1 anxiety disorder in the 12-month period prior to the interview. Of them, 28% had received any treatment in the previous year and 10% had received possibly adequate treatment. Only 41% of those with anxiety disorders had perceived a need for treatment, and of these, 67% had received any treatment in the previous year (Alonso et al. 2018). In an earlier review, a treatment gap of 56-58% for panic disorder, GAD and OCD was found (Kohn et al. 2004).

In the National Comorbidity Survey Replication, 37% of participants with 12-month anxiety disorders had used healthcare services. Of those treated patients, 34% had received minimally adequate treatment (Wang et al. 2005b). The NCS-R also showed that 50-95% of those with lifetime anxiety disorders (panic disorder, agoraphobia, GAD, PTSD, social phobia and specific phobia) eventually make treatment contact. Delays were long, ranging from 9-20 years for anxiety disorders, the longest delays concerning social phobia (16 years) and specific phobia (20 years) (Wang et al. 2005a).

In the Canadian Community Health Survey, among participants with panic disorder, agoraphobia and social phobia, 37% had used health services in the past 12 months. Overall, 21% had received adequate treatment. Criteria for minimally adequate treatment were slightly less strict than usual, requiring only 7 outpatient visits in the past 12 months and anxiolytic or antidepressant medication without a minimum time limit. Those with comorbid anxiety or depressive disorders and difficulties in social situations were more likely to receive adequate treatment. Other factors associated with treatment adequacy were being aged 25-54 years, a high school or post-secondary education level, being unmarried, living in an urban area, having medical insurance and having accepting attitudes toward illness and the healthcare system. (Roberge et al. 2011)

In the ESEMeD in 6 European countries, a total of 8.4% had experienced an anxiety disorder (OCD excluded) during the previous 12 months, and 20.6% of these participants had sought help from the healthcare system in the past 12 months (Alonso et al. 2007). Another study reported that treatment adequacy of treated anxiety disorders was 55% (Fernández et al. 2007). In the Spanish sample, about 41% of those with at least one depressive or anxiety disorder (GAD, PD and social phobia) had used services during the past year. The proportion of treatment was highest for panic disorder (49%) and depressive episode (49%) and the lowest for social phobia (31%), being 42% for any anxiety disorder. Treatment adequacy was assessed by an expert panel in addition to previously mentioned criteria. The probability of receiving minimally adequate treatment was almost the same for any anxiety disorder (31%) and depressive episode (36%), and was clearly lowest in panic disorder (25%). In this study, correlates of treatment adequacy were high educational level, a good self-rated health state and living in a large city (Fernández et al. 2006).

Finnish population-based studies

In the Finnish Health 2000 Study, generalized anxiety disorder, agoraphobia, panic disorder with or without agoraphobia and social phobia were included in the assessment of anxiety disorders. The prevalence of healthcare service use among subjects with these anxiety disorders was 36%, which was almost the same as those with MDD. Greater perceived disability, psychiatric comorbidity, younger age and parental psychiatric problems predicted use of services (Hämäläinen et al. 2008). Sihvo et al. investigated different types of treatment among subjects with anxiety disorders and found that among those using healthcare services for mental health reasons (34%), 80% had received pharmacotherapy and 45% had only received psychological treatment. Pharmacotherapy only treatment was associated with living in a semi-urban area, retirement and high perceived disability, whereas higher education and comorbidity with mood disorders predicted psychological treatment (Sihvo et al. 2006). In the earlier Mini Finland Health Survey of 1980, 26.1% of those with anxiety and phobic neurosis had received psychiatric treatment (Lehtinen et al. 1990a).

Studies among adolescents and young adults

The National Epidemiologic Survey on Alcohol and Related Conditions in the US during 2001-2002 found a prevalence of 12-13% for anxiety disorders among young adults aged 19-25 years. Panic disorder, social anxiety disorder, specific phobia and generalized anxiety disorder were included in the study. Only 16% of college students and 12% of non-college attending peers with anxiety disorders had used mental health services in the past year, which was much less than those with mood disorders (34%). (Blanco et al. 2008)

In another US web-based survey concerning university students, the PHQ anxiety module was used to screen symptoms of generalized anxiety and panic disorder. Overall, 63% of those with comorbid depression and anxiety and 52% of those with pure anxiety had used either medication or therapy/counselling in the past year. Hence, in this study, those with only anxiety symptoms sought help more often than those with pure depression. (Eisenberg et al. 2007)

2.5.3 DROP OUT FROM MENTAL HEALTH TREATMENT

Clinical studies have shown that problems in mental healthcare are often related to continuity of treatment, as drop out usually weakens the effectiveness of treatment (Killaspy et al. 2000; Melartin et al. 2005). Drop out may be associated with sociodemographic or clinical features as well as be a sign of poor functioning of the healthcare system (Young et al. 2000). Hence, for improving healthcare services it is important to know which factors constitute a risk to continuity of treatment.

The World Mental Health Survey investigated drop out from mental healthcare in the past 12 months in 24 countries worldwide and found an overall drop-out rate of 32%, ranging from 26% in high-income countries to 45% in upper-middle-income countries. The drop out was less common from psychiatric care than other sectors and across country income groups. Drop out was also more likely early in treatment, after one or two visits, whereas it was less likely if there had been prior treatment and if there were three or more providers. These factors may indicate severity and chronicity of a disorder, whereas patients with more need for treatment drop out less (Wells et al. 2013). On the other hand, they may also reflect the fact that experienced stigma may be especially strong among new patients and enhance discontinuation of treatment (Olfson et al. 2009).

The National Comorbidity Survey Replication in the United States showed that 22% of patients who had received treatment in the previous 12 months discontinued treatment prematurely. Again, drop-out rates were lowest for treatment by psychiatrists, and most drop outs occurred after the first or second visit. Mental health insurance was related to lower rates of discontinuation, but the relationship between patient characteristics and drop out was complex, varying between different treatment sectors and phases of treatment (Olfson et al. 2009). A similar drop-out rate (22%) was found in the Canadian Community Health Survey for those with mental health treatment during the past year. In contrast to NCS-R, discontinuation was most common for those treated by psychiatrists. A risk of drop out was increased in non-white persons and those aged 15-25 years, as well as participants with mood disorders or substance dependence (Wang 2007). In the European Study of the Epidemiology of Mental disorders, the situation was slightly better among those with depression and anxiety: only 14% of those with mental health treatment in the past year dropped out. The figures

were almost the same for psychiatrists, psychologists and general practitioners (20%). Discontinuation was more common during the first three visits to general practitioners and psychologists, and less common among those with older age, female gender or living in large or midsize urban areas (Pinto-Meza et al. 2011).

O`Brien et al. reviewed 14 studies on disengagement from mental health services and found drop-out rates varying from 4-46 %, depending on the study setting, service type and definition of engagement used. They concluded that associations between sociodemographic and clinical factors and disengagement are complex and multifaceted, as there are only a few consistent predictors in different studies. In the studies reviewed, sociodemographic factors, such as young age, ethnicity and deprivation, clinical variables, including lack of insight, substance misuse and forensic history, and variables related to service provision seemed to play a role in disengagement (O'Brien et al. 2009). Another review focusing on studies of treatment adherence in anxiety disorders found no consistent sociodemographic or clinical features associated with non-adherence. However, expectations and opinions about treatment were related to adherence in panic disorder, social anxiety disorder and obsessive-compulsive disorder. Hence, the authors emphasize that healthcare systems should consider expectations and beliefs about the disease and treatment, in order to motivate patients to participate in treatment even before it begins (Santana and Fontenelle 2011).

2.6 SUMMARY OF THE LITERATURE REVIEW AND GAPS IN KNOWLEDGE

Depressive and anxiety disorders are prevalent disorders often having a chronic or fluctuating course. According to population-based studies, prognosis of these disorders is more favourable than in clinical studies. While figures of persistence and recurrence are rather well documented, less is known about their effect on other outcomes, such as quality of life.

Disorder-related factors, such as severity of illness and comorbidity, have often been related to a poor prognosis of these disorders, but there are mixed findings on many other factors, such as sociodemographic, gender and age. Especially rare are studies on cognitive functioning as a predictor of prognosis in depressive and anxiety disorders in the general population. Less is also known about the consequences and course of these disorders, when the onset of disorder is before or during young adulthood.

Despite the many negative impacts of depressive and anxiety disorders at individual and population level, they are often undetected and undertreated. Delays in treatment seeking are long and drop out from treatment is common, leading to low rates of minimally adequate treatment worldwide. However, predictors of treatment may vary in different healthcare systems.

Therefore, knowledge of treatment received and related factors in Finland is needed to develop the Finnish healthcare system.

The prevalence of depressive and anxiety disorders is highest in late adolescence and early adulthood, which is a critical life stage of identity formation and socialization. However, studies focusing on the treatment of anxiety disorders among young adults in recent years are especially rare, though untreated mental disorders at this age may be particularly harmful.

3 AIMS OF THE STUDY

The present thesis investigated treatment and outcomes of depressive and anxiety disorders among young adults in a population-based sample.

The specific aims of the study were to examine in a population-based sample:

1. Treatment adequacy for depressive disorders; treatment seeking and discontinuation; and sociodemographic and clinical features associated with receiving or discontinuing treatment among young adults (Study I)
2. Treatment adequacy for anxiety disorders; treatment seeking and discontinuation; and sociodemographic and clinical features associated with receiving or discontinuing treatment among young adults (Study II)
3. The outcome of depressive and anxiety disorders; and sociodemographic and treatment-related factors and scales assessing mental health predicting the outcome (Study III)
4. Neuropsychological test performance as a predictor of outcome of depressive and anxiety disorders (Study IV)

4 SUBJECTS AND METHODS

4.1 STUDY DESIGN

4.1.1 THE HEALTH 2000 SURVEY

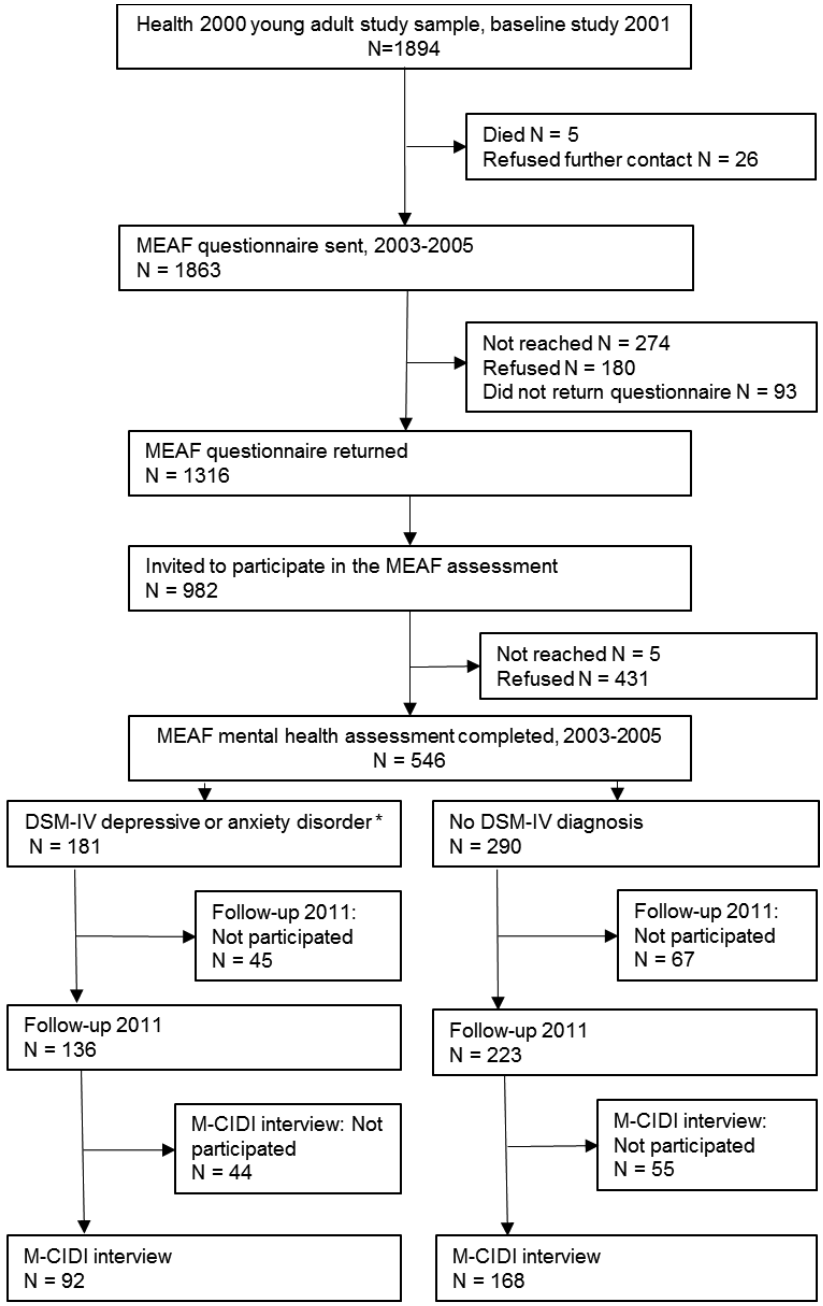
The study sample was derived from the Mental Health in Early Adulthood in Finland Study (MEAF) (Suvisaari et al. 2009), an in-depth examination of the Health 2000 young adult study sample focusing on mental health. The Health 2000 Survey was a comprehensive health survey in which target population consisted of individuals aged 18 or over and living in mainland Finland on July 1st 2000. The two-stage, stratified cluster sample comprised 9922 persons aged 18 or over, of whom 8028 persons were aged 30 or over (the adult sample) and 1894 persons aged 18-29 years (the young adult sample) (Aromaa et al. 2004; Heistaro and Kansanterveyslaitos 2008).

The original young adult assessment was carried out in 2001 and involved the use of an interview and a questionnaire to gather information on sociodemographic factors, childhood and school experiences, health, use of medication and health services, and lifestyle. There were also questions related to mental health, but no structured clinical interview was conducted for the young adult sample, in contrast to the adult sample (Pirkola et al. 2005) who were interviewed with the Munich Composite International Diagnostic Interview (M-CIDI) (Wittchen et al. 1998a). Therefore, a substudy focusing on the mental health of young adults (MEAF) was carried out (Suvisaari et al. 2009).

4.1.2 THE MENTAL HEALTH IN EARLY ADULTHOOD IN FINLAND STUDY

MEAF had a two-phase study design. In the first phase, a questionnaire was sent 2-4 years after the original study to all members of the young adult sample, excluding those who had died or refused further contact. In the second phase, a part of the sample was selected to the interview based on responses to the questionnaire and on information from the Finnish Hospital Discharge Register (Suvisaari et al. 2009). The study flow of the MEAF study is presented in Figure 2.

Figure 2. The study flow of MEAF and the 2011 follow-up of MEAF participants with depressive and/or anxiety disorders or no DSM-IV diagnosis at baseline



*Subjects with schizophrenia spectrum psychotic disorders or a specific phobia without other depressive or anxiety disorders excluded

4.1.2.1 The MEAF questionnaire and screen for mental health interview

MEAF mental health screen questionnaire was designed to screen for all current and lifetime mental disorders. It contained questions on education, occupation, social relationships, general health, alcohol and tobacco use and several scales assessing mental health and substance use. The Kessler Psychological Distress Scale (K10) (Kessler et al. 2003a) and the General Health Questionnaire (GHQ-12) (Goldberg et al. 1997) were used to detect general psychological stress. The Mood Disorder Questionnaire (MDQ) (Hirschfeld et al. 2000) was used for manic symptoms, SCOFF (Sick, Control, One stone, Fat, Food) questionnaire (Morgan et al. 1999) for eating disorders and CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire (Mayfield et al. 1974) for alcohol abuse. The psychosis screen consisted of 22 questions of delusions and hallucinations from the M-CIDI (Wittchen et al. 1998a). All participants who reported symptoms above a defined threshold in any screening scale were asked to take part in the mental health interview (Suvisaari et al. 2009). Screens are presented in Table 2. Number of persons selected by screens is presented in Table 1 in original Study I.

Table 2. Screens used for selecting persons to mental health interview in the Mental Health in Early Adulthood study

Screen	Time limit of symptoms	Symptoms that the screen assesses	Cut-off point or criterion for selection
General Health Questionnaire (GHQ-12)	Past month	Psychological distress	>3
Kessler Psychological Distress Scale (K10)	Past month	Psychological distress	>18
SCOFF Questionnaire	Current	Eating disorders	>1
Munich Composite International Diagnostic Interview (M-CIDI) section G	Lifetime	Psychotic disorders	At least one symptom
Mood Disorder Questionnaire (MDQ)	Lifetime	Bipolar spectrum disorders	>6
CAGE Questionnaire	Lifetime	Alcohol use disorders	>2
Use of any illicit drug	Lifetime	Substance use disorders	At least 6 times
Suicide attempt	Lifetime	Severe suicidality	At least one attempt
Use of health services for mental health problem	Lifetime	All mental disorders	At least once
Perceived need for treatment	Lifetime	All mental disorders	Self-reported need for treatment
Hospitalization due to any mental health disorder	Lifetime	All mental disorders	ICD-10 group F or ICD-8 and ICD-9 290-319

Persons with a history of suicide attempt were also considered screen positive, as well as participants who had reported use of any illicit drug at least six times. Additionally, all people who reported previous or current treatment contact for mental health problems or perceived need for treatment were invited to the interview. Finally, information from the Finnish National Hospital Discharge Register (NHDR) was used to identify all participants who had received hospital treatment due to any mental disorder (ICD-10 section F, ICD-8 and ICD-9 290-319), and they were asked to take part in the interview. Persons who were selected via NHDR, but had not returned the MEAF questionnaire, were contacted through the person responsible for their treatment, usually their general practitioner or psychiatrist (Suvisaari et al. 2009).

Overall, 821 participants were screen positive based on the screening questionnaires/questions or hospital treatment and were invited to the second phase of the study. Of them, 458 (55.8%) participated. A random sample of screen-negative participants, 161 out of 548 (29.4%), were also asked to participate in the interview, of whom, 88 (54.7%) participated (Suvisaari et al. 2009).

Non-participation occurred in both phases of the study; in the questionnaire and in the interview. Women, younger participants and those who had finished high school were more likely to return the MEAF questionnaire, whereas those with hospital treatment because of a mental disorder, according to the Hospital Discharge Register, returned it less often (Suvisaari et al. 2009).

Of screen positives, women and those who had completed high school participated more often in the MEAF interview, whereas less likely to participate were those who had been treated in a mental or general hospital for mental health problems, according to the Finnish Hospital Discharge Register. However, participants and non-participants did not differ in any of the questionnaire screens used for the mental health interview (Suvisaari et al. 2009).

4.1.2.2 Mental health assessment

The mental health assessment was conducted using the research version of the Structured Clinical Interview for DSM-IV (SCID-I) (First et al. 2001), which began with the SCID screening module to enhance reliability (Kessler 2007). The sections on mood, psychotic symptoms, substance use, anxiety and eating disorders were used in the SCID interview.

The mental health assessment began with a neuropsychological test battery, which was selected to evaluate attention, working memory, learning and memory, executive functioning and general cognitive ability (Castaneda et al. 2008a). The interview included questions on sociodemographic factors and treatment received for mental health problems, followed by the SCID-I interview and questions assessing lifetime occurrence of suicidal ideation

and behaviour. Current psychological functioning was evaluated by the Global Assessment of Functioning (GAF) and current social and occupational functioning by Social and Occupational Functioning Assessment Scale (SOFAS) (APA 2000a). Experienced research nurses or psychologist, who had attended 1-week training and regular follow-up sessions, conducted the interviews, which were reviewed together with a psychiatrist once or twice monthly. After the interview, participants were given another questionnaire for further information on their mental health and associated factors.

All case records from hospital and outpatient treatment contacts were obtained with the participants' approval for the final diagnostic assessment. The Finnish Ministry of Social Affairs and Health gave permission to go through the case records of non-participants, excluding those who had refused any participation in the Health 2000 study. Additionally, in order to gather information on all lifetime treatments for mental health disorders, information from the Hospital Discharge Register, self-reported mental healthcare contacts and primary healthcare centres was used. The final best estimate diagnoses using DSM-IV-TR criteria were made by four experienced clinicians (Jaana Suvisaari, Terhi Aalto-Setälä, Samuli Saarni, Jonna Perälä), who systematically evaluated all available information from the interview and/or case records. Disorders not covered by SCID-I, including all personality disorders, were also assessed. Personality disorder was diagnosed if DSM-IV-TR criteria for personality disorder were met according to case records and/or interview.

All four clinicians evaluated 40 cases to test the reliability of the diagnoses: unweighted Kappa values between each pair of raters ranged from 0.94 to 1.00 for major depressive disorder, from 0.90 to 1.0 for any depressive disorder, from 0.94 to 1.00 for any anxiety disorder, from 0.94 to 1.00 for alcohol abuse or dependence, from 0.48 to 1.00 for eating disorders and from 0.51 to 0.78 for personality disorders.

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the Health 2000 Survey as well as the MEAF reassessment. After receiving a complete description of the study, participants gave written informed consent. (Aromaa et al. 2004)

4.1.3 THE HEALTH 2011 SURVEY

The Health 2011 Survey is a follow-up study of the Health 2000 Survey (Koskinen et al. 2012). All participants of the Health 2000 Survey, who were alive, living in Finland and who had not previously refused any further contact, were invited to take part in the follow-up. The participants of Health 2000 young adult sample, who were 29-40 years in 2011, were also invited. Additionally, there was a new random sample of young adults aged 18-28 (Heistaro and Kansanterveyslaitos 2008). Only the original sample of young adults who participated in the MEAF study was included in this study. The follow-up 2011 study flow of MEAF participants is presented in Figure 2.

Information was collected with a health examination and interview and several self-administered questionnaires related to health, functional ability and lifestyle. A telephone interview was offered for those who were not able to participate in the health examination. Additionally, register-based information on all people in the sample was linked to the survey data. Data were collected in August–December 2011. Complementary data collection (home interview with shortened health examination or telephone interview) was conducted between January and June 2012. (Lundqvist and Mäki-Opas 2016)

In the Health 2011 Survey, mental health assessment was performed with the Munich Composite International Diagnostic Interview (M-CIDI) (Wittchen et al. 1998a), which was carried out in the health examination. This version of M-CIDI assessed the 12-month prevalence of eight diagnoses based on the criteria of DSM-IV: panic disorder, agoraphobia, social phobia, generalized anxiety disorder, dysthymia, major depressive disorders, alcohol abuse and alcohol dependence.

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the Health 2011 Survey. Participants provided written informed consent after receiving a complete description of the study. (Koskinen et al. 2012)

4.2 PARTICIPANTS

4.2.1 STUDY I

In the MEAF mental health assessment, 145 persons (17.7%) fulfilled the DSM-IV criteria for lifetime unipolar depressive disorders (Suvisaari et al. 2009). Participants with a diagnosis of schizophrenia spectrum psychotic disorder (3 persons) were excluded. Thus, the final sample comprised 142 participants with unipolar depressive disorders. Of them, 111 participants (78.2%) had major depressive disorder, 4 (2.8%) had dysthymia and 30 (21.1%) had depressive disorder NOS.

4.2.2 STUDY II

In the MEAF assessment, 95 (12.6%) participants received a diagnosis of anxiety disorder. Excluding those with a diagnosis of schizophrenia spectrum psychotic disorder (N=3), left 92 participants with a diagnosis of anxiety disorders. Among these participants, the most prevalent anxiety disorder was panic disorder, affecting 27.2% (N=25) of participants, followed by social phobia (25.0%, N=23), anxiety disorder NOS (25.0%, N=23) and specific phobia (20.7%, N=19). Agoraphobia without panic disorder (7.6%, N=7), post-traumatic stress disorder (6.5%, N=6), obsessive-compulsive disorder

(5.4%, N=5) and generalized anxiety disorder (3.3%, N=3) were less common (Table 2 in the original Study II).

Participants with specific phobia had treatment statistically significantly less often than other anxiety disorders (Table 3 in the original Study II). This phenomenon that patients with isolated phobias very rarely seek professional help has been observed previously (Bandelow et al. 2014). Because of the lesser clinical significance and a different treatment model (Choy et al. 2007; Guidelines Advisory Committee 2006), participants whose only anxiety disorder was a specific phobia (N=13) were excluded. Hence, for treatment analyses, the sample size was 79 participants.

4.2.3 STUDY III AND IV

Participants of Study III and IV comprised those young adults who at baseline had a lifetime diagnosis of depressive or anxiety disorder or both. This group is referred to as the DAX group. After excluding persons with a specific phobia as the only anxiety disorder, the sample size was 181 persons.

Out of these 181 participants, 136 persons (75.1%) took part in at least one part of the follow-up study in 2011, and 92 (50.8%) participated in the M-CIDI interview (Figure 2). When comparing those MEAF participants who did or did not participate in a M-CIDI interview in 2011, women and those with a higher education were found to have participated more often. However, there were no differences between follow-up participants and non-participants in psychiatric symptoms at baseline based on mental health screens (K10, GHQ-12, MDQ and CAGE).

The control group of Study III consisted of those participants of the MEAF study who did not receive any DSM-IV diagnosis at baseline (N=290). Of this group, 223 participants (76.9%) took part in at least one part of the Health 2011 Survey, while 168 (57.9%) persons participated in the M-CIDI interview (Figure 2). Overall, of participants aged 29-40 years old during the Health 2011 study, 61.4% participated in at least one part of the survey (Lundqvist and Mäki-Opas 2016).

4.3 TREATMENT OF DEPRESSIVE AND ANXIETY DISORDERS

4.3.1 OUTCOME VARIABLES

4.3.1.1 Minimally adequate treatment (Studies I and II)

For treatment of depressive and anxiety disorders, one of the main aims was to determine the proportion of participants who had received minimally

adequate treatment and to identify possible affecting factors. Information on treatment had been asked in the MEAF interview. In addition, medical records were reviewed for additional information concerning the treatment as a part of this thesis.

Criteria for minimally adequate treatment were determined according to evidence-based guidelines (APA 1998; APA 2000b; Guidelines Advisory Committee 2006; Koran et al. 2007; NICE 2004; Ursano et al. 2004). They were basically the same as those used in the ESEMeD and NCS-R studies (Fernández et al. 2007; Wang et al. 2005b), except for hospital treatment and anxiolytic medication. Hospitalizations had not been used as an adequacy criterion previously, but here, information was available on hospitalizations based on the National Hospital Discharge Register and corresponding case records. Such information had not been available in previous studies. The evaluation period in Finland is four days and, according to information from case records, it was considered as sufficient time to assess the diagnosis as well as to plan and start treatment. This time limit also excluded short visits to emergency departments. Because of these reasons, at least 4 days of hospitalization was chosen as an adequacy criterion.

Guideline-concordant treatment for depressive disorders in this study was defined as follows:

1) Pharmacotherapy: use of antidepressant for at least 2 months and at least four visits within 12 months with a physician for depressive disorders. Telephone consultations between patient and physician, as well as consultations between healthcare professionals and the treating physician concerning the patient's treatment were also included in visits.

2) Psychotherapy: at least eight sessions within 12 months with a psychiatrist, psychologist or psychotherapist in any setting or with another professional in a psychiatric clinic for depressive disorders.

3) Hospital treatment: at least 4 days of hospitalization for depressive disorders.

Thus, guideline-concordant treatment here does not mean that every step of the guidelines had been accomplished.

Treatment was assessed minimally adequate if pharmacotherapy, psychotherapy or hospital treatment was defined to be guideline concordant.

For anxiety disorders, criteria for minimally adequate treatment were the same in other respects, but buspirone was also accepted as adequate pharmacotherapy. Unlike the ESEMeD and NCS-R studies, benzodiazepine use for at least 2 months was not accepted as an appropriate pharmacotherapy for anxiety disorders, because the benefits and disadvantages of long-lasting use of benzodiazepines are controversial (Cloos and Ferreira 2009; Dell'osso and Lader 2013; Lader 2014).

4.3.1.2 Use of mental health services and treatment received (Studies I and II)

Information on mental health service use and treatment received for depressive and anxiety disorders was gathered from mental health interviews and case records. Visits and medication use were evaluated during the 12 months that a participant was most intensively treated if the treatment period had lasted over a year. All data were collected on the most recent and the most intensively treated episode of depression and the most recent and the most intensive treatment period for anxiety disorders. However, since the aim was to investigate the typical and the most recent functioning of the healthcare system, this thesis focuses on treatment received during the most recent depressive episode or the most recent treatment period for anxiety disorders.

All available information was used to determine minimally adequate treatment and its components. We counted the visits with physicians and professionals in the mental healthcare sector and evaluated the duration of medication based on the information in the case records, if they were available. Only the visits related to the mental health, and wherever possible visits specifically related to depressive or anxiety disorders, of participants were considered. If case records were missing or incomplete, the visits and medication use were estimated based on the interview which included questions about the type, duration and frequency of treatment.

Visits with physicians related to depressive or anxiety disorders were counted and divided into three categories: none, at least one visit or at least four visits within 12 months. A session of psychotherapy was defined as a visit with a psychiatrist, psychologist or psychotherapist in all settings or a visit with any professional in a psychiatric clinic. Therefore, the professional was not necessarily a psychotherapist and we could not evaluate the duration of sessions. Thus, psychotherapy in our study signifies broad psychosocial support instead of actual psychotherapy. Sessions of psychotherapy were counted and divided into three categories: none, at least one session or at least eight sessions within twelve months.

Pharmacotherapy was evaluated for the type and duration, and the information on medication use was divided into three categories: not prescribed, prescribed, or prescribed and used for at least two months. For participants with anxiety disorders, benzodiazepine use and misuse was also evaluated. Misuse was recorded if the subject had a diagnosis for benzodiazepine abuse or dependence, or had told about misuse in the interview or during the treatment period. Only misuse during the index treatment period was evaluated. Information on hospitalizations, their cause and duration was also gathered.

Treatment drop out was judged if the treatment was planned to continue according to the case records, but the patient discontinued the visits by their own decision.

4.3.2 POSSIBLE BASELINE PREDICTORS OF TREATMENT RECEIVED

4.3.2.1 Sociodemographic factors (Studies I and II)

Sociodemographic information was obtained from the mental health interview. For studying the relationship between sociodemographic factors and treatment the following variables were used: gender, marital status, age at the time the MEAF questionnaire was sent, basic education and current employment. Age at the time the MEAF questionnaire was sent was divided into age groups of 19–24 years, 25–29 years and 30–34 years old. Basic education consisted of two categories: less than high school and high school (matriculation examination completed). As some of the younger members of the cohort had not yet finished their vocational or higher education, only the effect of basic education was examined. Current employment was divided into four categories: 1) employed; 2) student; 3) unemployed and 4) other. The "other" employment group consisted of participants who were at home taking care of household and family members, on disability pension or sick leave or on return to work trial after sickness absence.

4.3.2.2 Disorder-specific factors of depressive disorders (Study I)

For depressive disorders, the relationship between available disorder-specific factors and treatment was also examined. The duration of depressive episode was defined broadly based on the information from the case records. Having a diagnosis of major depressive disorder was chosen as an indicator of the severity of a disorder. The lifetime history of suicide attempt had been evaluated based on self-reported suicide attempt in the MEAF questionnaire and/or SCID-I interview or suicide attempt according to case records (Suokas et al. 2011).

4.3.2.3 Comorbid psychiatric disorders (Studies I and II)

The effect of comorbid psychiatric disorders on treatment was also investigated. In the case of depressive disorders, three main categories of non-psychotic disorders were used: anxiety disorders, substance use disorders and eating disorders. For anxiety disorders, the following comorbid disorder categories were used: mood disorders, substance use disorders, personality disorders and "Other disorders", referring to psychotic, eating, sleeping, adjustment and impulse control disorders. The impact of a number (one or more) of different anxiety disorders on treatment was also examined.

4.4 OUTCOME OF DEPRESSIVE AND ANXIETY DISORDERS

4.4.1 OUTCOME VARIABLES

4.4.1.1 M-CIDI diagnosis of depressive or anxiety disorders in 2011 (Studies III and IV)

In Studies III and IV, the main outcome variable was a diagnosis of depressive or anxiety disorder based on the M-CIDI-interview in 2011. The interview assessed 12-month prevalence of eight diagnoses based on the criteria of DSM-IV: panic disorder, agoraphobia, social phobia, generalized anxiety disorder, dysthymia, major depressive disorder, alcohol abuse and alcohol dependence. Information on the mental health status of participants was not available between the baseline and follow-up study. Therefore, the disorders in 2011 may have been chronic or recurrent, or the disorder may have transformed to another type of depressive or anxiety disorder.

4.4.1.2 Self-estimated quality of life (Study III)

The other outcome variable in Study III was a self-estimated quality of life in 2011. It was measured by a single-item question, where participants were asked to evaluate quality of life with 5-step scale. For this study, the answers were divided into two categories: 1) response categories very bad, bad, and neither good nor bad and 2) response categories good and very good.

4.4.1.3 Level of education (Study IV)

In Study IV, the level of education was also used as an outcome measure. The information on the level of education in 2011 was received in the structured interview and was based on the highest level completed. Educational level was divided into two categories: 1) basic level (no high school or vocational school) or intermediary level (completed high school or completed vocational school) and 2) high level (a degree from a higher vocational institution, polytechnic or university).

4.4.2 POSSIBLE BASELINE PREDICTORS OF OUTCOME

4.4.2.1 Sociodemographic factors (Study III)

Information on sociodemographic factors at baseline included the same variables used in Studies I and II. The relationship between gender, basic education, marital status and employment status at baseline and outcome of depressive and anxiety disorders in the follow up was investigated.

4.4.2.2 Diagnostic group and comorbidity (Study III)

Participants were divided into three groups based on their diagnoses at baseline: 1) those who had only depressive disorders without anxiety disorders; 2) those who had only anxiety disorders without depressive disorders and 3) those who had both depressive and anxiety disorders.

4.4.2.3 Treatment (Study III)

The effect of treatment on the outcome of depressive and anxiety disorders was also investigated using two variables formed in Studies I and II: having received any treatment and having received minimally adequate treatment.

4.4.2.4 Mental health screens (Study III)

In the MEAF baseline study, several scales were used to assess mental health and substance use of the participants. Of those scales, K10 (Kessler et al. 2003a), GHQ-12 (Goldberg et al. 1997), MDQ (Hirschfeld et al. 2000) and CAGE (Mayfield et al. 1974) questionnaires, measuring different dimensions of vulnerability, were chosen to be possible predictors of outcome of depressive and anxiety disorders. In addition, anxiousness was measured using a single question ("trait anxiety" asking: "Are you usually tense or distressed?") that has been used to measure anxiousness in previous Finnish studies (Fröjd et al. 2007). The answer categories were: 1) "I have good control over my feelings and do not become tense or distressed easily"; 2) "I do not feel tense or distressed"; 3) "I become distressed quite easily"; 4) "I become anxious, tense or distressed very easily" and 5) "I feel anxious or tense all the time as if I have lost my nerves".

4.4.2.5 Neuropsychological test performance (Study IV)

The neuropsychological test battery at baseline included internationally used, well-validated test methods, which have all been validated in the Finnish normal population. They were administered in a fixed order and were scored

following standardized procedures by one psychologist (A.E.C) blind to the presence of diagnoses. A selection of tests that describe cognitive performance as comprehensively as possible were chosen as possible outcome predictors.

The Vocabulary subtest of the Wechsler Adult Intelligence Scale, Revised (WAIS-R) was used to measure general intelligence, and the Digit Symbol subtest to assess visuomotor performance and processing speed (Wechsler 1981). Attention and executive functioning were evaluated with the Trail Making Test (TMT), parts A and B (Reitan and Wolfson 1993). Attention and working memory were measured using the Digit Span Forward and Backward subtests (auditory attention) and the Visual Span Forward and Backward subtests (visual attention) of the Wechsler Memory Scale, Revised (WMS-R) (Wechsler 1987). The California Verbal Learning Test (CVLT), including the parts of immediate, short-delay and long-delay recall as well as recognition hits, was used to evaluate verbal learning and memory (Delis et al. 1987). Descriptions of neuropsychological tests are presented in Table 3.

Table 3. Description of neuropsychological tests

Test	Description	Cognitive function
WMS-R Digit Span Forward	Immediate recall of digit series increasing in length	Auditory attention and working memory
WMS-R Digit Span Backward	Immediate recall of digit series in reverse order increasing in length	Auditory attention and working memory
WMS-R Visual Span Forward	Immediate recall of spatial location patterns increasing in length	Visual attention and working memory
WMS-R Visual Span Backward	Immediate recall of spatial location patterns in reverse order increasing in length	Visual attention and working memory
WAIS-R Vocabulary	Explaining the meaning of words	General intelligence
WAIS-R Digit Symbol	Drawing corresponding symbols under digits according to a key provided as fast as possible in 90 seconds	Visuomotor performance and processing speed
Trail Making part A	Drawing a line to connect numbers in circles in an ascending order as fast as possible	Attentive and executive functioning
Trail Making part B	Drawing a line to connect numbered and lettered circles alternating between two sequences and in an ascending order as fast as possible	Attentive and executive functioning
CVLT immediate recall	Learning and recall of a list of 16 words on five trials	Verbal learning and memory
CVLT short-delay recall	Recall of the original list after a recall of an interference list	Verbal learning and memory
CVLT long-delay recall	Recall of the original list after a delay of 20 to 30 minutes	Verbal learning and memory
CVLT recognition hits	Recognition of original words in the list	Verbal learning and memory

4.5 STATISTICAL METHODS

4.5.1 STUDIES I AND II

In Studies I and II, sociodemographic factors and other characteristics of participants were compared between genders using the chi-square test or Fisher's exact test when appropriate (expected cell count less than 5 in a 2x2 table). Survey weights were not used, since the analysis was limited to the small subgroups of participants with depressive or anxiety disorders. The relationship of sociodemographic factors, comorbid psychiatric disorders and disorder-specific factors (Study I) was examined separately for different components of care, treatment adequacy and discontinuation of treatment using the chi-square or Fisher's exact tests when appropriate. Finally, logistic regression analyses were used to identify variables that were independently

associated with the type and adequacy of treatment. Possible predictors were entered simultaneously into a logistic regression model to explore the factors affecting treatment. All statistical tests were two-tailed, and values of $p<0.05$ were considered statistically significant. The SAS 9.3 statistical package was used in the analyses.

4.5.2 STUDIES III AND IV

In Studies III and IV, the sampling design and attrition in all stages, especially in the follow-up study in 2011, had to be accounted for in the statistical analysis. That is why inverse probability weights (IPWs) applied in the Health 2011 Survey were used to adjust for the effect of non-participation. Weighting also corrects the distribution of known background factors in the group of participants to match the distribution in the population. Sociodemographic information from Statistics Finland and data from the baseline survey were used to create inverse probability weights. Based on this information, participation probabilities were estimated by a logistic regression model, and then calibrated regarding known population distributions (Härkänen et al. 2016).

In Study III, characteristics of the participants of the DAX group, who had a 12-month diagnosis of depressive or anxiety disorder in 2011, were first compared to those who were in remission in 2011. The difference in sociodemographic factors, alcohol risk use, self-estimated quality of life and psychiatric medication between these groups was tested using the $\chi 2$ test with weights or Fisher's exact test when appropriate. The same variables and methods were also used to compare participants of the DAX group to those without any DSM-IV diagnosis at baseline.

To study whether categorical variables, such as sociodemographic factors, diagnostic group or treatment variables, were associated with the persistence/recurrence of depressive or anxiety disorder or self-estimated quality of life, a chi-squared test using weights or Fisher's exact test were used to analyse differences between groups. Concerning scales assessing mental health which were continuous variables, Student's t-test was used for between-group comparisons.

To identify variables that were independently associated with outcome of depressive or anxiety disorders, logistic regression analysis was used. Possible predictors of outcome were entered simultaneously into a logistic regression model, and weights were used to account for non-response.

In Study IV, the association between baseline cognitive functioning and the persistence/recurrence of depressive and anxiety disorders and the educational level of participants in 2011 was studied. Because of the continuous baseline variables, Student's t-test was used to analyse differences between groups.

All statistical tests were two-tailed. Values of $p<0.05$ were considered statistically significant. The SAS 9.3 statistical package was used to carry out the analyses.

5 RESULTS

5.1 TREATMENT OF DEPRESSIVE DISORDERS (STUDY I)

5.1.1 CHARACTERISTICS OF PARTICIPANTS

The study sample consisted of 142 young adults with any lifetime depressive disorder, 45 (31.7%) male and 97 (68.3%) female. Approximately half of them were married or cohabiting (N=69) as well as having completed high school (N=67). The smallest age group was those under 25 years old (21.8%, N=31), while groups of 25-29 years old (N=53) and those who were at least 30 years old (N=58) each accounted for about 40% of the sample. Almost 60% (N=89) of participants were employed, whereas about one fifth (N=29) were students, 13.1% (N=18) belonged to the "Other" employment group and 7.3% (N=10) were unemployed. (Table 2 in the original Study I)

The majority (78.2%, N=111) of participants had a diagnosis of major depressive disorder, and 12.0% (N=17) had a history of suicide attempt. One third (N=41) of disorders had continued over a year. About a third (N=46) of participants had comorbid anxiety disorders, 19.0% (N=27) had substance (alcohol) use disorders and 8.5% (N=12) had eating disorders. Of all participants, 10.6% (15) were currently (during the last month before the interview) in their most recent depressive episode. The median time between the beginning of the last depressive episode and the survey was 2.3 years. (Table 2 in the original study I)

Women had statistically significantly better basic education than men. Men were more often employed or unemployed, whereas women belonged more often to student or "other" groups concerning employment. Men had more often comorbid substance use disorders, while women had more often eating disorders. There were no other statistically significant gender differences in sociodemographic factors, disorder-specific factors or comorbid disorders. (Table 4)

Table 4. Sociodemographic and disorder-specific factors and comorbid psychiatric disorders of MEAF participants with a diagnosis of lifetime depressive disorder, excluding those with schizophrenia spectrum disorder

		MEAF participants with a diagnosis of lifetime depressive disorder (N=142)				
		Men (N=45)		Women (N=97)		
Variable	**Category**	**%**	**N**	**%**	**N**	**p[b]**
Age	<25 years	20	9	23	22	
	25-29 years	40	18	36	35	
	≥30 years	40	18	41	40	0.89
Basic education	Less than high school	64	25	45	44	
	High school	36	14	55	53	**<0.05**
Current employment	Employed	70	28	54	52	
	Student[e]	15	6	24	23	
	Unemployed	15	6	4	4	
	Other[a]	0	0	19	18	**<0.01**
MDD[d]		80	36	77	75	0.72
Suicide attempt		16	7	10	10	0.37
Duration of depression >1 year		29	10	36	31	0.52
Comorbid anxiety disorder[d]		31	14	33	32	0.82
Comorbid substance use or dependence (alcohol)[d]		42	19	8	8	**<0.0001**
Comorbid eating disorder[d]		0	0	12	12	**<0.01[c]**

[a] Of the other group, 5.6% (1) were on disability pension and 94.4% (17) at home taking care of household
[b] The p-values indicate a significance of the difference between genders in the distribution of each category tested by $\chi 2$ or Fisher's exact test. P-values <0.05 in boldface
[c] Fisher's exact test was used in the analysis
[d] A lifetime disorder

5.1.2 TREATMENT RECEIVED AND TREATMENT ADEQUACY

Of participants with depressive disorders, 76.1% (N=108) had had some kind of contact with the healthcare system for their depression. A total of 40.9% (N=58) of subjects had received minimally adequate treatment. About two-thirds (N=92) of participants had visited a physician at least once and 28.5% (N=39) had had at least four visits in twelve months. Antidepressive medication had been prescribed to 43.7% (N=62) of participants, and a little less than a third had used it for at least two months. Guideline-concordant pharmacotherapy including physician visits was received by 17.6% (N=25) of participants. Approximately 60% (N=84) of subjects had attended psychotherapy sessions, a third (N=47) at least eight times in twelve months.

Of all participants, 9.2% (N=13) had received hospital treatment, and 7.0% (10 participants) had stayed in the hospital at least four days. Five of them had also received minimally adequate treatment in outpatient care. About 16% (18) had discontinued visits by their own decision despite an adequate treatment plan. (Figure 3)

Two of the participants with a diagnosis of MDD had psychotic features. Both of them fell into the category of minimally adequate treatment according to the criteria of this study. One of them had antipsychotic medication. Case records were not available for the other participant to ascertain the medication. In the interview, this participant mentioned only antidepressive medication, though treatment had been otherwise intensive including almost daily visits in outpatient care.

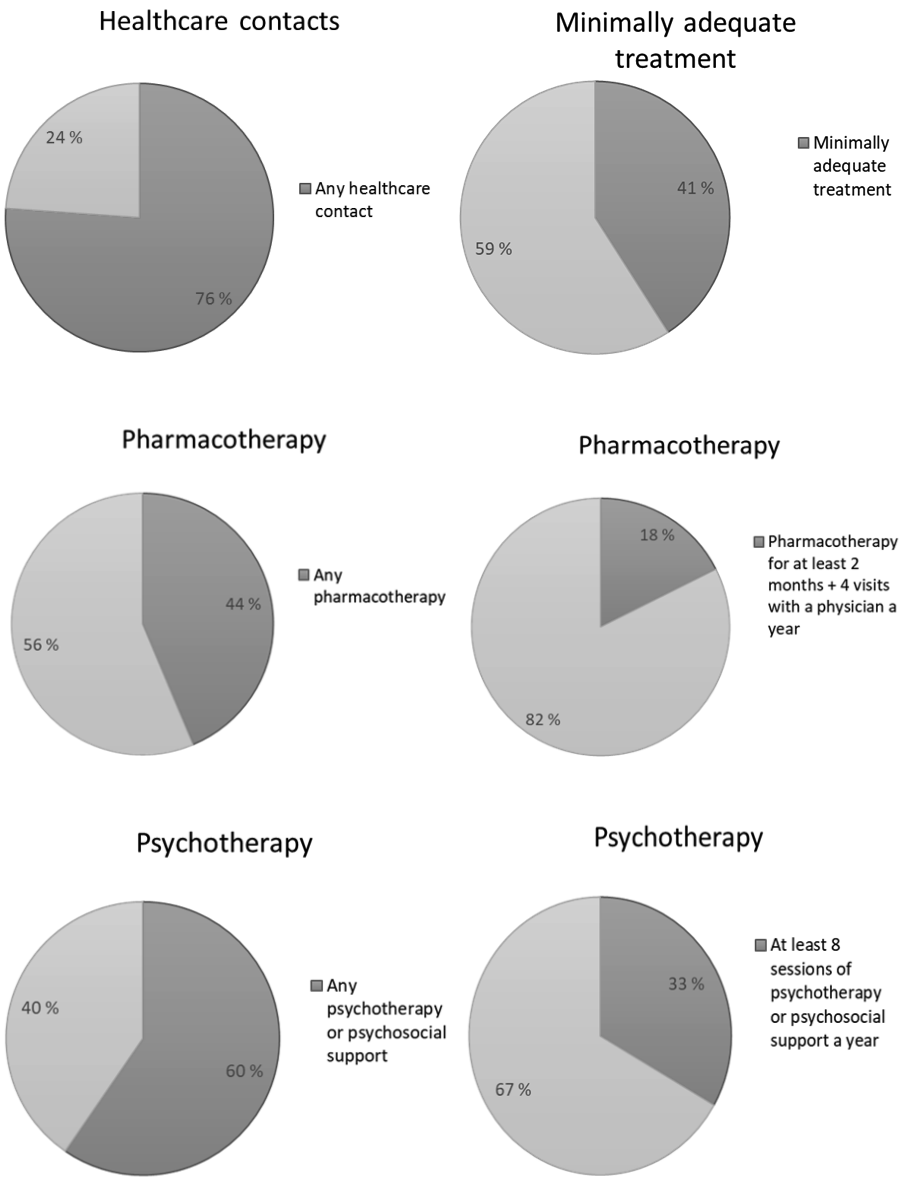


Figure 3. Healthcare contacts, minimally adequate treatment, pharmacotherapy and psychotherapy received for depressive disorders

5.1.3 SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH TREATMENT

In the bivariate analysis, psychotherapy was statistically significantly associated with gender and employment group: at least eight sessions of psychotherapy in 12 months had been received by women more often than men (39.6% vs. 20.0%, p=0.022), and those in the employment categories "Students" or "Other" more often than employed or unemployed (48.3% and 50.0% vs. 26.6% and 10.0%, p=0.026). As regards education, those who had completed high school had no visits with a physician more often than those with lower education (43.1% vs. 23.9%, p=0.019). (Table 3 in the original Study I)

Age group at the time of the study was widely associated with treatment in the bivariate analysis: the youngest age group had received minimally adequate treatment (61.3% vs. 32.1% and 37.9%, p=0.027) and most aspects of it statistically significantly more often than the older participants. (Table 3 in the original Study I)

5.1.4 DISORDER-SPECIFIC FACTORS AND COMORBID PSYCHIATRIC DISORDERS ASSOCIATED WITH TREATMENT

Severity of a disorder was statistically significantly related to treatment: those with a diagnosis of MDD had more often four visits with a physician in 12 months (33.0% vs. 12.9%, p=0.029) as well as pharmacotherapy for at least two months (36.1% vs. 14.3%, p=0.027) than others. Duration of depressive episode (>1 year or ≤1 year) was associated with minimally adequate treatment (68.3% vs. 26.3%, p<.0001) and also with different components of treatment in the bivariate analysis. (Table 4 in the original Study I)

Of comorbid disorders, only comorbid alcohol use disorder was associated with treatment according to the bivariate analysis: those with alcohol use disorder had at least one visit with a physician within 12 months more often than the rest of the sample (84.0% vs. 63.4%, p=0.047). (Table 4 in the original Study I)

5.1.5 SOCIODEMOGRAPHIC AND DISORER-SPECIFIC FACTORS AND COMORBID PSYCHIATRIC DISORDERS ASSOCIATED WITH TREATMENT DROP OUT

Of the study group, 15.7% (N=13) dropped out from treatment despite an adequate treatment plan. According to bivariate analysis, those with a history of suicide attempt (60.0% vs. 11.4%, Fisher's exact p<0.001), comorbid alcohol disorder (38.9% vs. 11.3%, p=0.008) and less education (22.2% vs. 3.6%, p=0.003) discontinued their visits more often than others. (Table 3 and Table 4 in the original Study I)

5.1.6 FACTORS ASSOCIATED WITH TREATMENT AND DROP OUT IN MULTIVARIATE ANALYSES

According to multivariate analysis, female gender was associated with treatment in several aspects: women had higher odds of having at least one visit with a physician (OR 4.45, CI 1.58–12.54, p=0.005), at least one session of psychotherapy (OR 2.53, CI 1.04–6.16, p=0.041) and at least 8 sessions of psychotherapy a year (OR 3.37, CI 1.20–9.46, p=0.021). Additionally, those with alcohol use disorders had higher odds of having at least one visit with a physician in 12 months (OR 8.29, CI 1.69–40.58, p=0.009). In the multivariate analyses, the severity of a disorder also remained a significant predictor: MDD was associated with higher odds of having at least 4 visits with a physician in 12 months (OR 5.44, CI 1.40–20.12, p=0.014). Those in the age group 25–29 years had the lowest odds of having any medication (OR 0.20, CI 0.07–0.57, p=0.003) and guideline-concordant medication (OR 0.30, CI 0.10–0.92, p=0.035), as well as at least one visit with a physician (OR 0.18, CI 0.05–0.63, p=0.008) compared to the youngest age group. (Table 5 in the original Study I)

Multivariate analyses were also used to study the possible predictors of drop out from treatment. A history of suicide attempt was associated with increased odds of discontinuing treatment (OR 6.73, CI 1.10–41.17, p=0.039). In contrast, participants who had completed high school had lower odds of treatment interruption (OR 0.15, CI 0.03–0.86, p=0.033). (Table 5 in the original Study I)

5.2 TREATMENT OF ANXIETY DISORDERS (STUDY II)

5.2.1 CHARACTERISTICS OF PARTICIPANTS

The sample of participants with a lifetime diagnosis of any anxiety disorder consisted of 66 (71.7%) women and 26 (28.3%) men. Almost half (N=42) of participants had finished high school, and two-thirds (N=59) were married or cohabiting. Currently employed were 56.2% (N=50) of participants, 11.2% (N=10) were unemployed and 18.0% (N=16) were students. Almost 15% (N=13) of participants belonged to the “Other” employment group, i.e. they were at home taking care of household and family members, on disability pension or sick leave, or on return to work trial after sickness absence. Almost 60% (N=54) of the sample had a comorbid mood disorder, a fifth (N=20) had comorbid personality disorders and 28.3% (N=26) had substance use or dependence. Almost 19% (N=17) had other lifetime disorders (psychotic, eating, sleeping, adjustment or impulse control disorders). (Table 1 in the original Study II)

Of those with a diagnosis of comorbid personality disorder, one participant had three, one subject had two and 18 persons had one personality disorder. The most common personality disorder was Personality

disorder not otherwise specified, which affected 11 persons. Nine participants received a diagnosis of borderline personality disorder, whereas diagnoses of schizotypal, paranoid and avoidant personality disorders were each received by one person. The figures were the same after excluding those with a diagnosis of specific phobia without other depressive or anxiety disorders.

Male participants had statistically significantly more often a comorbid substance use disorder than female participants. There were no other statistically significant gender differences in sociodemographic factors or in comorbid disorders. (Table 5)

Panic disorder was the most common anxiety disorder with 27.2% (N=25) of the sample. Social phobia and anxiety disorder NOS both affected 25.0% (N=23) of participants, followed by specific phobia affecting 20.7% (N=19). Agoraphobia without panic disorder (7.6%, N=7), post-traumatic stress disorder (6.5%, N=6), obsessive-compulsive disorder (5.4%, N=5) and generalized anxiety disorder (3.3%, N=3) were less common. (Table 2 in the original Study II)

Participants with anxiety disorder NOS had statistically significantly more often some treatment than others (p=0.001). In contrast, those with specific phobia were more often without treatment. (Table 3 in the original Study II)

Table 5. Sociodemographic factors and comorbid psychiatric disorders of MEAF participants with a lifetime diagnosis of anxiety disorder, excluding those with schizophrenia spectrum disorder and specific phobia without other anxiety disorder

		MEAF participants with a lifetime diagnosis of anxiety disorder (N=92)				
		Men (N=26)		Women (N=66)		
Variable	**Category**	**%**	**N**	**%**	**N**	**p[b]**
Age	<25 years	15	4	21	14	
	25-29 years	42	11	39	26	
	≥30 years	42	11	39	26	0.82
Basic education	Less than high school	70	16	47	31	
	High school	30	7	53	35	0.06
Current employment	Employed	70	16	52	34	
	Student[e]	22	5	17	11	
	Unemployed	9	2	12	8	
	Other[a]	0	0	20	13	0.08[c]
Married or cohabiting		57	13	70	46	0.25
Comorbid mood disorder[f]		62	16	58	38	0.73
Comorbid personality disorder[f]		31	8	18	12	0.19
Comorbid substance abuse or dependence[f] (any substance)		**58**	15	**17**	11	**<0.0001**
Other disorders[d]		8	2	23	15	0.14

[a] Of the other group, 10 (76.9%) were at home taking care of household and family members, 2 (15.4%) were on disability pension or sick leave and 1 (7.7%) was on return to work trial after sickness absence
[b] The p-values indicate a significance of the difference between genders in the distribution of each category tested by $\chi 2$- or Fisher's exact test. P-values <0.05 in boldface
[c] Fisher's exact test was used in the analysis
[d] Psychotic, eating, sleeping, adjustment or impulse control disorder lifetime
[e] Students in vocational schools or universities
[f] A lifetime disorder

5.2.2 TREATMENT RECEIVED AND TREATMENT ADEQUACY

Before analysing treatment, those whose only anxiety disorder was a specific phobia (N=13) were excluded. After that, the sample size was 79 participants, 22 (27.9%) men and 57 (72.2%) women. Of them, 70.9% (N=56) had had some kind of contact with the healthcare system for their anxiety disorder, and 41.8% (N=33) had received minimally adequate treatment. Over half (N=40) of them had received pharmacotherapy (antidepressive medication or buspirone), and 43.4% (N=33) had used it for at least two months. Over two-thirds (N=53) had visited a physician at least once, and 36.4% (N=28) at least four times in 12 months. Guideline-concordant pharmacotherapy was

received by 26.6% (N=21) of subjects. Almost 60% (N=44) had attended a session of psychotherapy, 34.2% (N=26) at least 8 times a year (Figure 4). Of all participants, 11.4% (N=9) had been in hospital for their anxiety symptoms, and 10.1% (N=8) had had hospitalization for at least 4 days. Seven of them had also received minimally adequate treatment in outpatient care.

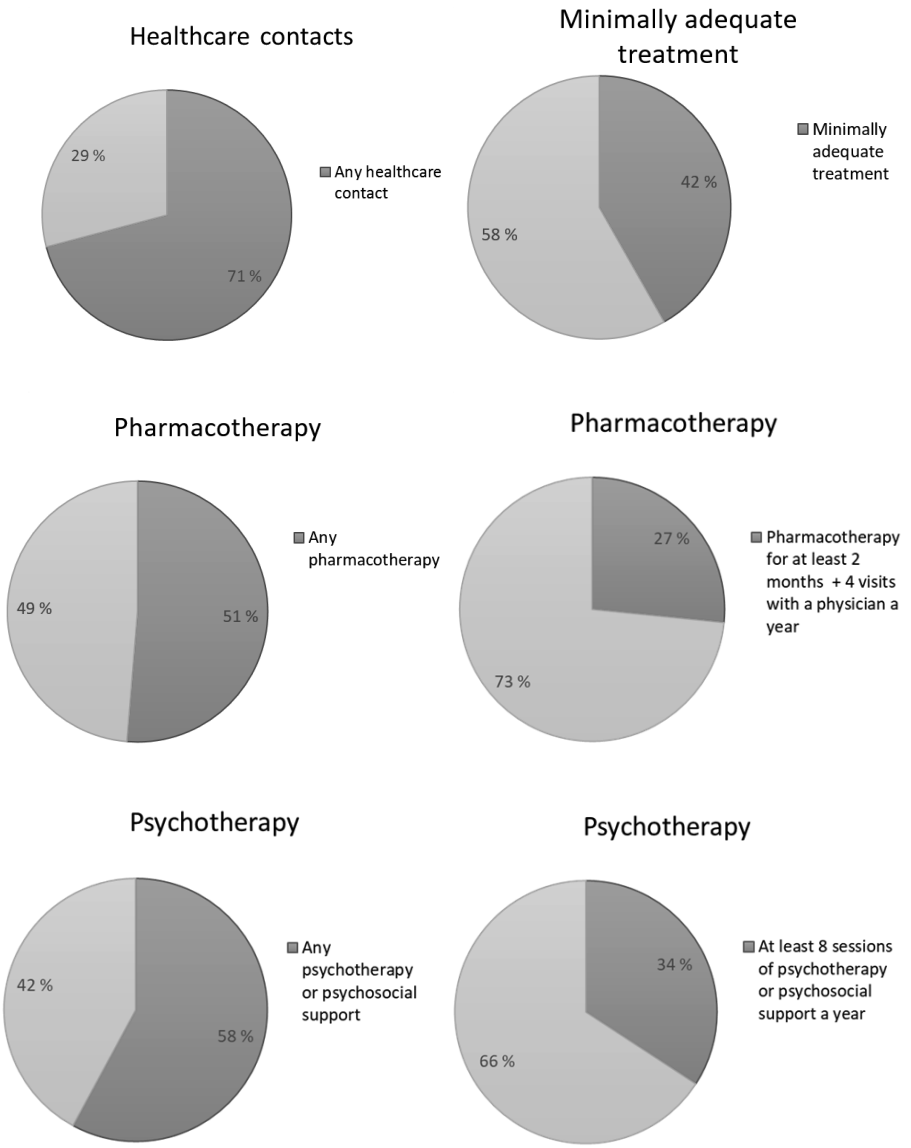


Figure 4. Healthcare contacts, minimally adequate treatment and treatments received for anxiety disorders

5.2.3 SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH TREATMENT

In the bivariate analysis, employment was statistically significantly associated with physician visits as well as psychotherapy: those who were currently employed had less frequently than others visited a physician at least 4 times in 12 months (22.5% vs. 57.1% and 62.5% and 30.8%, p=0.033) or attended psychotherapy sessions at least 8 times in 12 months (17.5% vs. 53.9% and 55.6% and 54.6%, Fisher's exact p=0.008). Those who were married or cohabiting had also visited a physician at least 4 times a year less often than those living alone (24.5% vs. 53.9%, p=0.011). Of the age groups, 25-29 years old participants had received less often at least eight psychotherapy sessions than other age groups (12.5% vs. 48.3% and 57.1%, p=0.002). (Table 4 in the original Study II)

5.2.4 COMORBID PSYCHIATRIC DISORDERS ASSOCIATED WITH TREATMENT

According to bivariate analysis, those with a comorbid substance use disorder had used more often than others antidepressive or buspirone medication for at least two months (63.6% vs. 35.2%, p=0.023), as well as benzodiazepine medication (56.5% vs. 25.5%, p=0.009). They also had received at least one session of psychotherapy statistically significantly more frequently than others (78.3% vs. 49.1%, p=0,018). (Table 5 and Table 6 in the original Study II)

Those with a comorbid personality disorder had visited a physician at least four times a year statistically significantly more often than others (57.9% vs. 29.3%, p=0.025). They also had more often than others benzodiazepine medication (57.9% vs. 23.7%, p=0.0004) as well as benzodiazepine misuse (20.0% vs. 0.0%, Fisher's exact p=0.003) according to bivariate analysis. Additionally, those with other comorbid disorders (lifetime psychotic, eating, sleeping, adjustment or impulse control disorders) had misused benzodiazepines statistically significantly more frequently than others (18.8% vs. 1.6%, Fisher's exact p=0.025). (Table 5 and Table 6 in the original Study II)

5.2.5 SOCIODEMOGRAPHIC FACTORS AND COMORBID PSYCHIATRIC DISORDERS ASSOCIATED WITH TREATMENT DROP OUT

Of participants with anxiety disorders, 11.0% (N=8) dropped out from treatment despite an adequate treatment plan. According to bivariate analysis, none of the sociodemographic factors or comorbid psychiatric disorders affected drop out. (Table 4 and Table 5 in the original Study II)

5.2.6 FACTORS ASSOCIATED WITH TREATMENT AND DROP OUT IN MULTIVARIATE ANALYSES

According to multivariate analysis, those who were married or cohabiting had lower odds of having at least four visits with a physician in 12 months than others (OR 0.27, CI 0.08-0.85, p=0.025). Comorbid substance use disorder was associated with antidepressive or buspirone medication for at least two months (OR 4.48, CI 1.11-18.08, p=0.035), while comorbid personality disorder was associated with benzodiazepine medication (OR 4.77, CI 1.11-20.59, p=0.036). None of the factors explained the final outcome of minimally adequate treatment, though the p-value was close to being significant for the association of being married or cohabiting and minimally adequate treatment (OR 0.36, CI 0.12-1.05, p=0.062). (Table 7 and Table 8 in the original Study II)

5.3 OUTCOME OF DEPRESSIVE AND ANXIETY DISORDERS (STUDIES III AND IV)

5.3.1 CHARACTERISTICS OF PARTICIPANTS FROM THE DAX GROUP

Of the DAX group, 92 participants had participated in the M-CIDI interview during the follow-up study in 2011, 25 (33.6%) men and 67 (66.4%) women. Altogether, 22.8% (N=22) of them had received a diagnosis of depressive or anxiety disorder still or again in 2011: 18.9% (N=18) of the DAX group had depressive disorders, 10.5% (N=10) anxiety disorders and 6.6% (N=6) had both disorders.

The majority (82.6%, N=76) of the sample were married or cohabiting. The level of education was high for 57.8% (N=58) and basic or intermediate for 42.2% (N=34) of the sample. Most (75.1%, N=69) of the participants were currently employed, while 7.6% (N=7) were students, 3.3% (N=3) unemployed and 14.1% (N=13) belonged to the “Other” group. Antidepressant medication was used by 13.0% (N=12), anxiolytic medication by 2.2% (N=2), hypnotic medication by 3.3% (N=3) and antipsychotic medication by 1.1% (N=1) of the DAX group. Over a quarter (N=25) had alcohol risk use measured by a 3-item AUDIT (Alcohol Use Disorders Identification Test) questionnaire using cut-off points ≥5 for women and ≥6 for men. Self-estimated quality of life was good or very good for 77.3% (N=68) of the sample (Table 1 in the original Study III). Those with a current M-CIDI diagnosis of depressive or anxiety disorder had a statistically significantly worse quality of life than those in remission in 2011. Otherwise, there were no significant differences between these two groups in sociodemographic factors, psychiatric medication use or alcohol risk use. (Table 6)

Table 6. Follow-up information of MEAF participants with a lifetime diagnosis of depressive or anxiety disorder (DAX group) who participated in the M-CIDI interview in 2011

Variable	Category	M-CIDI diagnosis of depression or anxiety in 2011 (N=92)				
		Yes (N=22)		No (N=70)		
		%[a]	N[b]	%[a]	N[b]	p[c]
Gender	Male	27	5	36	20	
	Female	73	17	64	50	0.46
Level of education	Basic, intermediary	46	9	41	25	
	High	54	13	59	45	0.72
Married or cohabiting	Yes	82	18	83	58	1.00 [d]
Current employment	Employed	68	15	77	54	
	Student	14	3	6	4	
	Unemployed	9	2	1	1	
	Other[f]	9	2	16	11	0.15 [d]
Self-estimated quality of life	Good or very good	41	9	89	59	
	Bad or very bad, not good, not bad	59	13	11	7	**<0.0001[d]**
Alcohol risk use[e]		43	9	22	16	0.06
Antidepressant medication use		9	2	14	10	0.72 [d]
Anxiolytic medication use		5	1	1	1	0.42 [d]
Hypnotic medication use		9	2	1	1	0.14 [d]
Antipsychotic medication use		5	1	0	0	0.24 [d]

[a] Percentages counted with weights except when Fisher's exact test used
[b] N-values counted without weights
[c] The p-values indicate a significance of the difference between categories in a distribution of diagnostic status tested by $\chi 2$ or Fisher's exact test. P-values <0.05 in boldface
[d] Fisher's exact test used
[e] Alcohol risk use measured by a 3-item AUDIT (Alcohol Use Disorders Identification Test) questionnaire using cut-off points ≥5 for women and ≥6 for men
[f] Of the "Other" group, 2 persons were on disability pension, 9 were at home taking care of household and family members and 2 persons were in a category "not specified"

5.3.2 COMPARISON OF PARTICIPANTS FROM THE DAX GROUP AND THE CONTROL GROUP IN 2011

The DAX group and the control group had a statistically significant difference in gender distribution: the DAX group consisted of 126 (62.8%) women and 55 (37.2%) men, while the control group comprised 150 (51.9%) women and 140 (48.1%) men. Level of education was higher in the control group, but there were no other statistically significant differences between

these groups in sociodemographic factors, such as marital status or current employment. (Table 7)

Of the DAX group, 22.8% (N=22) received a M-CIDI diagnosis of depressive or anxiety disorder in 2011, whereas for the control group this figure was 9.7% (N=16). This difference was statistically significant (p=0.005). These two groups also differed in self-estimated quality of life, which was statistically significantly better for the control group (Table 7). Furthermore, self-estimated quality of life was compared between three groups: 1) the control group; 2) participants of the DAX group who did not have a current depressive or anxiety disorder in 2011 and 3) participants with a current disorder in 2011. The proportion of those with good or very good quality of life in 2011 were almost similar in the first two groups (90.3% and 89.1%), but statistically significantly lower for those in the DAX group with a current disorder (39.6%) (p<0.0001).

Antidepressive medication use was more common in the DAX group, but there were no other statistically significant differences in psychiatric medication use. There was also no difference between the groups in alcohol risk use measured by a 3-item AUDIT. (Table 7)

Table 7. Follow-up information of the DAX group and the control group in 2011

		All (N=471)				
		Participants without any DSM-IV diagnosis at baseline (N=290)		Participants with depressive or anxiety disorder at baseline (N=181)		
Variable	**Category**	**%[a]**	**N[b]**	**%[a]**	**N[b]**	**p[c]**
Gender	Male	48	140	37	55	
	Female	52	150	63	126	**0.04**
M-CIDI diagnosis of depressive or anxiety disorder	Yes	10	16	23	22	
	No	90	152	77	70	**<0.01**
Level of education	Basic, intermediary	33	63	45	51	
	High	67	155	55	84	**0.03**
Married or cohabiting		79	175	75	106	0.37
Current employment	Employed	85	154	78	82	
	Student	4	7	8	9	
	Unemployed	3	6	3	3	
	Other[f]	8	17	12	16	0.33
Self-estimated quality of life	Good or very good	90	150	77	71	
	Bad or very bad, not good, not bad	10	16	23	21	**<0.01**
Alcohol risk use[e]		29	49	26	25	0.57
Antidepressant medication use		4	9	15	19	**<0.001**
Anxiolytic medication use		2	4	4	5	0.31 [d]
Hypnotic medication use		1	3	3	4	0.43 [d]
Neuroleptic medication use		1	2	1	1	1.00 [d]

[a] Percentages counted with weights except when Fisher's exact test used
[b] N-values counted without weights
[c] The p-values indicate a significance of the difference between categories in a distribution of diagnostic status tested by $\chi 2$ or Fisher's exact test. P-values <0.05 in boldface
[d] Fisher's exact test used
[e] Alcohol risk use measured by a 3-item AUDIT (Alcohol Use Disorders Identification Test) questionnaire using cut-off points ≥5 for women and ≥6 for men
[f] Of the "Other"-group, 2 persons were on disability pension, 26 were at home taking care of household and family members and 5 persons were in a category "not specified"

5.3.3 BASELINE PREDICTORS ASSOCIATED WITH PERSISTENCE OF DEPRESSIVE OR ANXIETY DISORDERS IN 2011

Sociodemographic factors at baseline were not related to receiving a M-CIDI diagnosis of depressive or anxiety disorder in the follow-up according to bivariate analyses in the DAX group. Persistence or recurrence of disorders

did not differ between groups with only depressive or anxiety disorders or a comorbid disorder at baseline. Neither having had any treatment nor adequate treatment predicted a diagnosis of these disorders in 2011. (Table 3 in the original Study III)

A higher score in the K10 questionnaire at baseline was associated with receiving a M-CIDI diagnosis of depressive or anxiety disorder in the follow-up (Mean 19.1 vs. 16.3, p=0.04). Scores in other questionnaires assessing mental health did not predict persistence or recurrence of these disorders in the bivariate analyses. (Table 4 in the original Study III)

5.3.4 BASELINE PREDICTORS ASSOCIATED WITH SELF-ESTIMATED QUALITY OF LIFE IN 2011

According to bivariate analyses, sociodemographic factors at baseline were not associated with self-estimated quality of life in the follow-up in the DAX group. There were also no differences in quality of life between diagnostic groups. Furthermore, having had any or adequate treatment did not predict quality of life in 2011. (Table 3 in the original Study III)

Concerning questionnaires that assessed mental health, the only statistically significant difference was that a lower score in the MDQ at baseline was related to better quality of life in the follow-up (Mean 3.1 vs. 5.6, p=0.02). (Table 4 in the original Study III)

5.3.5 PREDICTORS OF PERSISTENCE/RECURRENCE OF DEPRESSIVE OR ANXIETY DISORDERS AND QUALITY OF LIFE IN 2011; MULTIVARIATE ANALYSIS

Gender, basic education, marital status, treatment variables as well as scores in MDQ, K10 and CAGE questionnaires were chosen to be possible predictors of outcome. According to multivariate analysis, none of them predicted receiving a diagnosis of depressive or anxiety disorder in the M-CIDI interview in 2011. However, after adjusting for other factors, a lower score in the MDQ questionnaire at baseline was related to better quality of life in the follow-up (OR 0.82, 95% CI 0.69-0.97). (Table 5 in the original Study III)

5.3.6 NEUROPSYCHOLOGICAL TEST PERFORMANCE AS A PREDICTOR OF OUTCOME OF DEPRESSIVE AND ANXIETY DISORDERS (STUDY IV)

Performance in neuropsychological tests was not associated with the persistence or recurrence of depressive and anxiety disorders in bivariate analysis. Regression analysis was not done because of these negative initial results. (Table 1 in the original Study 4)

However, cognitive functioning at baseline was related to education at follow-up: those who had performed better in WMS-R Digit Span Forward subtest ($p<0.01$), WAIS-R Vocabulary subtest ($p<0.001$), WAIS-R Digit Symbol subtest ($p<0.001$), the CVLT immediate subtest ($p<0.05$) and short-delay ($p<0.05$) and long-delay recall ($p<0.01$) subtests, as well as both parts of the TMT ($p<0.01$), had higher education in the follow-up according to bivariate analysis.

6 DISCUSSION

6.1 SUMMARY OF THE MAIN RESULTS

This study investigated treatment adequacy and outcome of depressive and anxiety disorders among a Finnish population-based sample of young adults aged 20-34 years. The aims of the study were to describe treatments received for these disorders, and to define factors which were associated with treatment adequacy, different types of treatment and drop out from treatment. Furthermore, the aims were to examine the persistence or recurrence of lifetime depressive and anxiety disorders, their effect on the lives of affected persons after six to eight years of follow-up and to identify possible predictors of outcome.

Of young adults with depressive disorders, 76.1% had sought help for their disorder, and 40.9% had received minimally adequate treatment. The corresponding figures for those with anxiety disorders were very similar: 70.9% had sought treatment and 41.8% had received minimally adequate treatment.

None of the sociodemographic factors, disorder-related factors or comorbid psychiatric disorders explained receiving minimally adequate treatment in depressive or anxiety disorders. However, these factors associated with different components of treatment. Among those with depressive disorders, having a major depressive disorder was related to at least four visits with a physician a year, whereas female gender and comorbid substance use disorder were related to at least one visit with a physician in 12 months. Women were also more likely than men to receive any psychotherapy and at least eight sessions of psychotherapy. A lower level of education and a history of suicide attempt were related to dropping out from treatment.

Among participants with anxiety disorders, those who were currently married or cohabiting were less likely than others to have visited a physician at least four times a year. Comorbid substance use disorder was associated with having had antidepressant or buspirone medication for at least two months. Comorbid personality disorders were associated with both use and misuse of benzodiazepines.

Of young adults with depressive and/or anxiety disorders at baseline, 22.8% had these disorders in 2011 after six to eight years follow-up compared to a control group with no DSM-IV disorders at baseline. In 2011, the level of education was lower and quality of life poorer for those who had had these disorders at baseline than for those in the control group.

In the group who had a history of depressive or anxiety disorder at baseline, those who had a current depressive and/or anxiety disorder in the 2011 follow-up had a worse quality of life than those who were in remission.

Sociodemographic factors, disorder group, received treatment, scores in mental health screens or neuropsychological functioning did not predict persistence/recurrence of depressive and anxiety disorders, but higher score in MDQ at baseline, i.e. having had manic-like symptoms, was related to worse quality of life in the follow-up. Those with better neuropsychological test performance had a higher level of education in the follow-up.

6.2 TREATMENT OF DEPRESSIVE AND ANXIETY DISORDERS AMONG YOUNG ADULTS

6.2.1 TREATMENT SEEKING AND TREATMENT ADEQUACY

The proportions of treatment seeking and treatment adequacy were very similar for depressive and anxiety disorders. In both disorder groups, more than 70% had sought treatment for their disorder and over 40% had received minimally adequate treatment. In the Health 2000 study adult sample, only about one third of those with MDD and with anxiety disorders had used health services for mental health reasons. These figures suggest that young adults seek treatment more frequently than older adults in Finland (Hämäläinen et al. 2009; Sihvo et al. 2006). While previous studies on the treatment of depression among young people in Finland have shown treatment contact rates from one fifth to one third, this study suggests that treatment seeking of young people has increased in the last decades (Aalto-Setälä et al. 2002; Haarasilta et al. 2003). This may indicate the same trend as in the US, where treatment seeking was also improved and related stigma declined, especially among young people between 1990 and 2003 (Mojtabai 2007).

Detailed comparisons of mental health treatment between countries are challenging to do because relevant and valid data on mental health services are lacking (Wahlbeck 2011). There are also differences in study settings, criteria for minimally adequate treatment and anxiety disorders included between studies. Furthermore, most international studies have investigated 12-month disorders and gathered information only from interviews, in contrast to this study. Several population-based studies have found much lower rates of mental health service use among participants with depressive and anxiety disorders compared to this study. However, the results of most recent studies from Germany and the US are closer to our results, suggesting an increasing trend of help-seeking (Hasin et al. 2018; Mack et al. 2014). Figures of minimally adequate treatment have been lower than in this study, as most of the studies have found proportions of 15-22% for depressive disorders and even lower rates of 10-14% for anxiety disorders (Alonso et al. 2018; Duhoux et al. 2009; Eisenberg and Chung 2012; Fernández et al. 2006; Gabilondo et al. 2011; Wang et al. 2005b).

However, despite an increase in the treatment of depressive and anxiety disorders among young adults in Finland, there still is a large gap between healthcare use and minimally adequate treatment, which represents the minimum level of care that should be offered to everyone seeking treatment for these disorders.

6.2.2 PHARMACOTHERAPY

The results concerning medication use are in line with the same trend: in this sample, almost half of those with MDD had received antidepressant pharmacotherapy, whereas in the adult sample of Health 2000, 36.1% were currently receiving antidepressant medication (Hämäläinen et al. 2009). Among adolescents and young adults in the Finnish Health Care Survey 1996, use of antidepressants was less frequent, since only 14% had recently used antidepressants (Haarasilta et al. 2003). For those with anxiety disorders, the difference was even larger, as about half used antidepressant or buspirone medication in the young adult sample and 23% in the adult sample of Health 2000 (Sihvo et al. 2006).

Different register-based information reinforces the idea of increased use of antidepressant medication overall in Finland during the last decades (Sihvo et al. 2010; Terveyden ja hyvinvoinnin laitos 2018). During the same time, since 1990, the number of suicides has decreased possibly indicating better treatment outcome, though mortality of young people especially by suicide is still high in Finland by European comparison (Statistics Finland 2017). According to medication purchase register information, the relative share of reimbursement for depression medicine has been consistently much higher in those aged 25–64 years than in those aged 18-24 years. This contrast to our results may reflect a wide range of indications for use of antidepressant medication, for example, for pain and sleep, which may be more common in older age groups. During recent years, reimbursement for antidepressive medication has started to decline. Concurrently, recipients of rehabilitative psychotherapy have increased, maybe reflecting changes from 2011, when rehabilitative psychotherapy became a statutory benefit.

Benzodiazepines have been widely used in the clinical treatment of anxiety disorders despite controversy around possible physical dependency and an association with worse long-term outcomes (Cloos and Ferreira 2009). In this sample, benzodiazepines had been prescribed to 34.6% of participants with anxiety disorders. Benzodiazepine use was especially frequent among those with personality disorders and, according to bivariate analysis, those with substance use disorders. This is of concern because of the risk of paradoxical reactions, like increased anxiety, agitation and hyperactivity, and aggressiveness is known to be increased in these groups (Dell'osso and Lader 2013). Previously, benzodiazepine misuse has also been associated with other substance use problems (Dell'osso and Lader 2013). Misuse was not common in this study, but it may have been underestimated,

because a diagnosis by a treating physician or self-report in the interview was required. According to this study, more attention to prescribing of benzodiazepines is recommended. However, antidepressant or buspirone medication was prescribed to over half of those with anxiety disorders, which was even more frequent than for those with depressive disorders, suggesting that the trend is to use antidepressants as the first-line medication in anxiety disorders.

6.2.3 PREDICTORS OF TREATMENTS

None of the studied factors were related to receiving minimally adequate treatment in participants with depressive or anxiety disorders. The fact that sociodemographic factors did not affect treatment adequacy may be a positive sign reflecting the equality of the healthcare system in Finland. On the other hand, the healthcare system may not be working appropriately, because those with a higher risk of poor outcome, such as patients with more severe disorders and with comorbidities, did not receive minimally adequate treatment more often than others. However, among those with depressive disorders, comorbid substance use disorder and MDD were related to physician visits. For those with anxiety disorders, comorbid substance use disorders increased the probability of pharmacotherapy lasting at least two months. According to bivariate analysis, those with comorbid personality disorders were more likely than others to visit a physician at least 4 times in 12 months, and to also use and misuse benzodiazepines. Hence, there seems to be a trend to treat more intensively those with more complicated disorders, which may not always lead to adequate treatment, but sometimes to inappropriate use of benzodiazepine medication.

Among those with depressive disorders, women were more likely than men to visit a physician at least once a year and have sessions of psychotherapy or psychosocial support. This is in line with several studies, which have shown that women are more likely than men to seek, use and receive treatment (Alonso et al. 2004c; Briffault et al. 2008; Eisenberg and Chung 2012; González et al. 2010; Hämäläinen et al. 2009; Wang et al. 2005a; Wang et al. 2007a; Wang et al. 2007b). It has been suggested that women are more capable of translating feelings of distress into conscious recognition of having emotional problems, perceive less stigma and are therefore more acceptable to having treatment (Kessler et al. 1981).

Among those with anxiety disorders, currently married or cohabiting participants as well as those being employed had less often than others visited a physician at least 4 times a year, and employed participants were also less likely to have received at least 8 psychotherapy visits a year than other employment groups. This may indicate a trend of healthcare professionals to treat more intensively those with a higher risk of social exclusion. On the other hand, it may be due to the fact that anxiety disorders are a diverse group of disorders, where clinical significance changes with

varying severity. Hence, there may be a subgroup of participants who had milder symptoms, less disability, more social support and also more able to help themselves. Nevertheless, untreated anxiety disorders may lead to difficulties in academic, social and occupational functioning and cause personal suffering.

6.2.4 TREATMENT DROP OUT

In previous studies, the rates of drop out have varied widely from 4% to 46% from mental health service overall, and from 10% to 57% in anxiety disorders (O'Brien et al. 2009; Santana and Fontenelle 2011; Wells et al. 2013). Variation is large because of different study settings, service type and definitions related to drop out, which are not well conceptualized. The definition in this study was quite strict, because a plan to continue treatment was required in addition to the patient's decision to discontinue visits. However, the drop out rates of 16% for depressive disorders and 11% for anxiety disorders are in line with the ESEMeD, which found a drop-out rate of 14% among those with depressive and anxiety disorders during past 12 months (Pinto-Meza et al. 2011). Among those with depressive disorders, participants with suicidality and lower education dropped out more often than others. In a bivariate analysis, there was also an association between substance use and drop out as well as a relation between substance use and lower education with physician visits. Hence, it seems that a tendency to treat well these groups with complicated disorders does not always lead to adequate treatment, but to drop out from treatment. It is alarming, because these participants with wide-ranging problems are probably also at risk of social exclusion. Especially concerning is that participants with a history of suicidality dropped out more often than others, since previous suicide ideation and attempt are risk factors for further suicidality (Turecki and Brent 2016).

6.3 OUTCOME OF DEPRESSIVE AND ANXIETY DISORDERS

6.3.1 PERSISTENCE/RECURRENCE OF DEPRESSIVE AND ANXIETY DISORDERS

In this study, about a fourth of participants with depressive and/or anxiety disorders at baseline, that had follow-up information, had these disorders after 6-8 years, whereas the proportion was 10% in the control group which had no history of depressive or anxiety disorders at baseline. These figures show that anxiety and depressive disorders tend to persist. However, the result is quite favourable in comparison to many previous studies which have found lower remission rates. However, comparison of our findings with

previous studies is difficult, for example, because the follow-up times vary from months to several decades. The NEMESIS had a follow-up time of 7 years, which is close to ours, and found a lower remission rate of 61% for those with a 12-month CIDI diagnosis of depressive or anxiety disorders (Rhebergen et al. 2011).

6.3.2 PREDICTORS OF RECURRENCE/PERSISTENCE OF DEPRESSIVE AND ANXIETY DISORDERS

None of the chosen factors predicted persistence/recurrence of depressive and/or anxiety disorders. In previous studies, results concerning sociodemographic factors such as gender and age have been contradictory (Eaton et al. 2008; Markkula et al. 2016; Nay et al. 2013; Penninx et al. 2011; Scholten et al. 2013). In some studies, lower education, not being married and unemployment have been related to a worse outcome of these disorders (Batelaan et al. 2010a; Colman et al. 2007; van Beljouw et al. 2010). These associations were not found in this study. However, participants were young at baseline and had often not completed their education, and employment and marital status were not established.

Disorder-related factors, such as severity of illness or comorbidity, have often been found to predict the outcome of depressive and anxiety disorders (Beard et al. 2010; Hendriks et al. 2013; Markkula et al. 2016; Penninx et al. 2011). In this study, however, those with comorbid depressive and anxiety disorders did not have a worse outcome than those with pure disorders. Current symptom severity measured by K10 was associated with a persistence of disorders, but this result was not significant after adjustment.

Having had any treatment or adequate treatment were not related to persistence/recurrence of depressive and/or anxiety disorders. It may be that a limited effect of treatment does not show in a small sample. One can also speculate whether some aspects of treatment, such as benzodiazepine use or long sick leave, worsen the prognosis. It has been found previously that especially full-time sick leave for MDD may have negative consequences, as it seems to predict disability pension (Rytsälä et al. 2007; Viikari-Juntura et al. 2017). In Finland, sick leave and disability pension because of mental disorders, particulary depression, were increasing for a long time, and although the trend has only been declining since 2007, mental disorders are still the most prevalent disorder category for disability pension in the age group of 18-34 years (Finnish Centre for Pensions 2018; Järvisalo et al. 2005).

The absence of an association between treatment and outcome may also be due to a bias often seen in population-based studies: those with more severe disorders tend to seek treatment and to also receive intensive treatment more often than others (Bland et al. 1997; Prins et al. 2011a; Verhaak et al. 2009). Because severity is associated with receiving treatment, treatment may not be associated with better outcome or even be

paradoxically associated with worse outcome due to the confounding related to the severity of initial illness (Bruce et al. 2005; Spijker et al. 2001a; Spijker et al. 2001b). Castaneda et al. have previously found that depressed young adults with more impaired verbal memory and executive functioning were more likely to receive treatment in this sample (Castaneda et al. 2010). As cognitive functioning at baseline did not predict persistence/recurrence of depressive and/or anxiety disorders, it may indicate that treatment has been successful. However, deficits in neuropsychological test performance were very minor among those with depressive and anxiety disorders, possibly reflecting the fact that problems of cognitive functioning are more often seen in clinical- than population-based samples (Castaneda et al. 2008a; Castaneda et al. 2011).

6.3.3 EMPLOYMENT AND EDUCATION

Participants with a history of depressive or anxiety disorders had lower education in the follow-up compared to the control group, but a significant difference was not found in marital status and current employment. In the DAX group, there were more students and unemployed among those with current disorders, maybe indicating prolonged studies and work disabilities, but the difference was not statistically significant. Previously, depression has especially been seen to increase long-term work disability, unemployment, job turnover and presenteeism and absenteeism among employees (Hendriks et al. 2015; Lerner et al. 2004).

Some studies concerning adolescent depressive and anxiety disorders have found wide-ranging consequences, including difficulties in occupational functioning and also in family relationships in the follow-up (Essau et al. 2014; Fergusson and Woodward 2002). Based on this study, having these disorders before or during young adulthood seems to especially affect education, which is typically completed in young adulthood. Though this association has also been seen earlier, it cannot be disentangled whether mental disorders cause a lower level of education or if lower education is a risk factor for these disorders (Auerbach et al. 2016; Fergusson and Woodward 2002; Woodward and Fergusson 2001). Nevertheless, within the group of affected participants, better neuropsychological test performance at baseline predicted higher level of education in the follow-up as expected. These findings, together with Castaneda's studies, suggest that depressive and anxiety disorders in young adulthood probably affect educational achievement in other ways than by causing cognitive impairment. For example, typical symptoms of these disorders, like feelings of worthlessness, diminished interest, loss of energy and excessive worry, may reduce the ability to reach academic goals.

6.3.4 QUALITY OF LIFE

Participants with depressive and/or anxiety disorders at baseline had a lower self-estimated quality of life compared to the control group in 2011. Within the group of affected participants, those who also received a diagnosis of depressive or anxiety disorder in 2011 had lower quality of life than those in remission. This finding emphasizes the influence of a current disorder. In contrast, Markkula et al. found that among adult participants of the Health 2000 those who were depressed at baseline, but not in the follow-up, still had worse quality of life, measured by EQ-5D questionnaire, compared to the general population (Markkula et al. 2016). EQ-5D questionnaire also takes account of somatic symptoms and difficulties in taking care of oneself, which may appear as residual symptoms, especially among older adults. Nevertheless, there are some other studies which have shown that adequate mental health and global well-being, in terms of normal cognitive, social and role functioning, can be achieved after remission of depression (Kessler et al. 2003b; Koivumaa-Honkanen et al. 2008).

6.3.5 PREDICTORS OF QUALITY OF LIFE

The only predictor for quality of life was the MDQ questionnaire score: those with higher score in the MDQ questionnaire, reflecting more manic-like symptoms at baseline, had poorer quality of life in the follow-up. Benvenuti et al. also noticed in their study that hypomanic features in depressive disorders were associated with lower quality of life after remission (Benvenuti et al. 2015). Interestingly, Carta et al. found that being screen positive in MDQ was associated with worse subjective quality of life in a general population sample, and this was largely independent of comorbid conditions, such as mood, anxiety and eating disorders. Hence, they suggested that MDQ positivity identifies a specific area of discomfort that is "subthreshold" to psychiatric diagnosis (Carta et al. 2015). Baryshnikov et al. presented that the MDQ and McLean Screening Instrument for Borderline Personality Disorder measure partially the same dimensions in mood disorders (Baryshnikov et al. 2015). Paterniti et al. in turn found that MDQ items were higher when a stress-related condition, such as borderline personality disorder or PTSD, was present (Paterniti and Bisserbe 2018). In fact, there are many questions in MDQ which are related to emotion regulation and impulse control. Therefore, these abilities which help to control one's life may affect quality of life significantly.

6.4 STRENGTHS AND LIMITATIONS

The key strength of the study was the two-phase study design. It enabled conducting of SCID-I interviews, which require clinical judgement, as well as neuropsychological testing. Interviews were carried out by experienced

mental health professionals and neuropsychological tests by a psychologist. Information from interviews was complemented by medical records from mental health treatment contacts. Thus, the final diagnostic assessment was based on multiple sources of information, which compensated for possible effects of recall bias. This is exceptional in population-based studies. On the other hand, the results of this study cannot be directly compared to several previous studies, which have gathered information only from interviews. For some participants only medical records, and not SCID-I, were available. However, the figures of minimally adequate treatment were only slightly smaller (38.6% for depressive disorders and 37.1% for anxiety disorders) if the patients who had not been interviewed were excluded.

Concerning outcome studies, the main strength was a long follow-up period for depressive and anxiety disorders in a population-based sample. Focusing on young adults, especially their cognitive functioning, is rare in population-based studies.

The main limitation of two-phase study design and studies with a long follow-up is attrition. Non-response occurred with the questionnaire and the interview at baseline, as well as in the follow-up, especially the M-CIDI interview. Attrition in MEAF questionnaire and interview was related to age, gender and education, but not to self-reported mental health disorders or symptoms from the baseline survey. Participants with a lifetime history of hospital treatment for mental health problems returned the questionnaire and participated in the interview less often than others, but this was compensated by medical records obtained. However, non-participants and participants did not differ in any self-reported mental health disorders or symptoms at baseline screens.

A significant limitation in all substudies is a small sample size leading to low statistical power and wide confidence intervals, especially in logistic regression analyses. The small study sample did not allow studying of treatment for different anxiety disorders or different states of MDD, or outcome of different disorders or disorder groups separately. In addition, correction for multiple testing was not done in any of the substudies.

Concerning diagnostic assessment, a limitation is that SCID-II was not used. Thus, the final diagnoses of personality disorders were made by experienced clinicians using other available systematically evaluated information from the interview and/or case records.

In this study, the definition of dropping out from treatment was quite strict, requiring that treatment was planned to continue according to case records. However, case records were not always comprehensive in this regard, which led to several missing values in this variable. The same problem with missing values also concerned the variable describing the duration of depressive episode, which was estimated retrospectively based on information from case records and interviews.

A psychotherapeutic session in this study broadly represented psychosocial support, since there was no information on duration of sessions

or whether a provider was a licensed psychotherapist. Hence, access to actual psychotherapy cannot be estimated based on this study. Concerning pharmacotherapy, the dose of medication was not evaluated.

In this study, quality of life was measured by a single-item question. In previous studies, several multi-dimensional questionnaires have been used to measure health-related quality of life. It has been noticed that different measures may systematically emphasize different conditions (Saarni et al. 2006). On the other hand, in their study Zimmerman et al. found that a single-item question of quality of life was significantly correlated with the total scores and individual item scores of longer questionnaires. Therefore, they stated that a single-item question is a reliable, cost-effective and user-friendly measure and may be an excellent instrument in large population-based studies (Zimmerman et al. 2006).

6.5 CONCLUSIONS

In this study, treatment seeking of young adults with a history of lifetime depressive and anxiety disorders was relatively common compared to other previous studies. This suggests that young people may better recognize a need for treatment and may have more accepting attitudes towards mental health problems than older adults. Still, about a fourth of them had not had any contact with the healthcare system for their problems. Furthermore, over half of these young adults did not receive minimally adequate treatment, which everyone with a diagnosis of a depressive or anxiety disorder contacting the healthcare system should actually have. The moment a young person seeks treatment is critical to further treatment, emphasizing the importance of gatekeepers, such as professionals at school and student healthcare, as well as the primary healthcare system. Enough resources and education for mental health problems should be allocated to professionals providing treatment for young people.

As none of the sociodemographic factors were associated with receiving minimally adequate treatment, we can say that the healthcare system in Finland serves people equally. From a clinical point of view, however, the healthcare system should at least identify those with the most severe or complicated problems and offer adequate treatment to them. Thus, more efforts are needed to recognize and treat those people with a higher need for treatment.

Mental disorders of young people and education are in many ways intertwined. According to this study, lower education and suicidality were associated with dropping out from treatment among those with depressive disorders. This suggests that exclusion and lack of future view often expands into several areas of life. Hence, it is important to keep young people involved in society and to offer them hope and opportunity.

In clinical work, professionals on the front line, for example, in student healthcare, should pay attention to mental health problems, which may often appear indirectly as problems in studying or repeated visits with a physician for other reasons. Further intensive treatment should be offered, especially for those at risk of dropping out from the educational system. When treatment contact is initiated, special attention and frequent monitoring should be provided for those with a lack of future views, maybe showing as problems in education or as a history of suicidal attempt. Special attention for these risk groups may decrease drop out from treatment as well as prevent further suicidality (Turecki and Brent 2016).

Especially problematic are those young people who have already discontinued their studies, as they are out of reach of the educational system and health services related to them. Special efforts are needed to find them and motivate them to treatment. A recent review concluded that many young people, who may not otherwise have sought help, were accessing integrated youth healthcare systems, which combines physical health, mental health and social care services in a holistic manner (Hetrick et al. 2017). Integrative therapy interventions, such as dance-movement therapy, could also be useful methods to outreach and help young people (Koch et al. 2014).

Among those with anxiety disorders, there was a trend for those with personality disorders and substance use disorders to use benzodiazepines more frequently than others. These groups may be more vulnerable to the negative effects of benzodiazepines, which again may increase the risk of social exclusion. Hence, attention should be paid to prescription of benzodiazepines, and to emphasize antidepressants as first-line treatment of anxiety disorders.

Those with a history of lifetime depressive and/or anxiety disorders had lower education in the follow-up compared to the control group. As previous studies of this sample have shown very minor differences between these groups in cognitive functioning, there seemed to be other factors interfering with educational achievement in these disorders. Typical symptoms of these disorders, such as diminished interest, feelings of worthlessness, loss of energy and excessive worry are a challenge to succeeding in studies. Hence, healthcare and educational systems should work together supporting young people with mental health problems to continue their studies.

In clinical work, special attention should be paid to problems related to studies among young patients. Active interventions, such as supporting contacts to different educational institutions, should be carried out. Psychoeducation, giving hope and supporting educational goals could be implemented, as these disorders do not seem to significantly affect cognitive abilities in young age.

Educational policies should also support young people to continue and finish their education, and that way keep them up with society. Achieving a goal probably supports further activity, whereas dropping out may lead to repeated failures. Most students in high schools and vocational schools are at

an age when the risk of depressive and anxiety disorders is highest. Hence, they also need firm structure and predictability on their educational path to support their mental health. Therefore, changes made in educational policy should be consistent and well grounded, as precipitous and extensive changes to the system do not support mental health. Adolescents going to high school today should be entitled to know what the rules are when they apply to the next level of education. Because adolescents at high school age are psychologically still in the vulnerable developmental phase, too far-reaching and definitive decisions on future education should not be required of them. There should not be barriers to education, through which young people cannot go, for example, after recovery of depressive or anxiety disorders. Still, efforts to reduce stigmatization of people with mental problems are needed in the educational system.

In this study, none of the chosen factors predicted a persistence and/or recurrence of depressive or anxiety disorders, which is in line with many previous population-based studies where there have been mixed findings, especially for sociodemographic factors. Therefore, we cannot say who would need special attention, support or monitoring in the long term and allocate resources to them. On the other hand, it is a good thing that there were not factors, such as sociodemographic factors or cognitive abilities, which dictated a prognosis of a disorder. Hence, the healthcare system and patients themselves can do many things to affect the course of these disorders. There is some persistence and recurrence in depressive and anxiety disorders. Nevertheless, in this study, less than a fourth of young adults with a lifetime history of depressive or anxiety disorders had these disorders after the six to eight years of follow-up. These are encouraging issues to consider in the psychoeducation of young people with mental problems.

According to previous literature and this study, some policy implications may be made:

1. Adequate resources should be allocated to those working in the healthcare system with young people, such as school and student healthcare services.
2. Education on mental health problems among young people should be provided to different professionals working with adolescents and young people in different areas of life to raise awareness and reduce stigma.
3. Special support should be directed to the educational system to those with mental disorders and problems with studies.
4. Changes in educational policy should be predictable and well grounded, supporting educational achievement of vulnerable individuals.
5. In clinical work, special efforts are needed to engage patients with severe and multiple problems in treatment.
6. More attention should be paid to prescribing of benzodiazepines, especially for those with vulnerability to negative long-term effects.

7. Encouraging psychoeducation, emphasizing the possibility of recovery and the positive effect of one's own actions, should be given to young people with depressive and anxiety disorders.

Implications for further studies based on these results are to:

1. Examine barriers to treatment seeking and recent trends.
2. Identify reasons for not receiving minimally adequate treatment, as well as reasons for dropping out from treatment.
3. Investigate whether different treatment forms are related to outcome of depressive and anxiety disorders.
4. Identify reasons of lower educational achievement for people with depressive and anxiety disorders in young age.

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